HHS Public Access

Author manuscript

Neurosci Lett. Author manuscript; available in PMC 2021 November 07.

Published in final edited form as:

Neurosci Lett. 2021 November 01; 764: 136195. doi:10.1016/j.neulet.2021.136195.

The GM2 gangliosidoses: Unlocking the mysteries of pathogenesis and treatment

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Keywords

GM2; Gangliosidoses; Tay-Sachs disease; Sandhoff disease; Hexosaminidase A; HEXA; HEXB; Lysosomal storage diseases; Gene therapy

The GM2 gangliosidoses, Tay-Sachs (TSD), Sandhoff disease (SD) and GM2 activator deficiency are rare, progressive, neurodegenerative lysosomal storage disorders (LSDs) that are uniformly fatal and without effective therapy. The severe infantile form of TSD, originally termed *familial amaurotic idiocy,* was first described independently in 1899 by British ophthalmologist Waren Tay and New York neurologist Bernard Sachs in infants of Ashkenazi Jewish descent [1]. With the characteristic cherry red macula and multilamellar cytoplasmic bodies in neurons of affected patients, TSD is the prototype for the greater than 70 LSDs resulting from deficiencies in lysosomal hydrolases or transport proteins [2]. The clinical features and course of the disease were carefully chronicled by physicians at the Jewish Chronic Care Hospital in Brooklyn beginning in 1950. That same year families came together to support one another and exchange what they had learned in caring for their affected children and founded the National Tay-Sachs and Allied Diseases Association (NTSAD), the oldest patient advocacy group in the United States for rare genetic diseases. Although carefully described clinically and pathologically, the biochemical etiology of TSD was unknown until a deficiency of the enzyme β-hex osaminidase A isoenzyme (variously known as Hex A or β-N-ace-tylhexosaminidase αβ) was described by O'Brien et al. [3]. This enzyme is responsible for the degradation of the GM2 ganglioside, a complex glycosphingolipid particularly abundant in cell membranes in the nervous system.

The discovery of a deficiency in β-hexosaminidase A enzyme paved the way not only for diagnostic confirmation of affected infants, but through the heroic efforts of Dr. Michael Kaback, also led to carrier screening in the Ashkenazi Jewish community at synagogues

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

and community centers across the country beginning in the early 1970s. As a result, the incidence of infantile TSD among the Ashkenazim decreased by over 90% in just 10 years and TSD became a model for carrier screening among high-risk populations [4]. To assure the quality and accuracy of carrier screening, proficiency testing for academic and commercial laboratories was performed in the Kaback laboratory from 1973 to 2006 and continues at the University of Maryland laboratories with oversight and support from NTSAD.

In 1968 Konrad Sandhoff described an infant whose clinical presentation matched Tay-Sachs disease but had additional visceral accumulation of the neutral glycolipid globoside and complete absence of β-hexosaminidase activity [5]. Sandhoff went on to identify two forms of the enzyme, the A and B isoforms, both of which were absent in his patient [5,6]. This finding was contrary to patients with TSD who typically only lacked activity for the A isoform. These observations paved the way for further studies that determined that β-hexosaminidase A was a heterodimer enzyme composed of an alpha and a beta subunit (αβ) (Fig. 1) and β-hexosaminidase B was a homodimer from two beta subunits (ββ). The presence of the β subunit in both forms of the enzymes accounted for the complete lack of β-hexosaminidase activity in his and others similarly affected patients later designated as having Sandhoff disease [7–9]. Only the β-hexosaminidase A has biological activity against the GM2 substrate. Whereas TSD has an increased carrier frequency in the Ashkenazi Jewish population (1 in 27) compared to a much lower worldwide carrier frequency of 1 in 250–300, Sandhoff disease is pan ethnic with a carrier frequency of 1 in 1,000,000 [10–12].

Cloning of the *HEXA* gene, coding for the alpha subunit of the β-hex- osaminidase A enzyme in 1984 by Proia and Myerowitz [13] led to the discovery of the common infantile Ashkenazi mutations in 1988 [14–17]. A total of 101 pathogenic mutations in *HEXA* have now been described worldwide [18]. With its ease and availability, gene sequencing has largely replaced enzymatic testing and is now the preferred method for carrier screening as reflected in a recent policy statement by NTSAD [19]. Cloning of the *HEXB* gene, coding for beta subunit of the β-hexosaminidase A enzyme (and the two subunits of β-Hexosaminidase B) was achieved in 1985.[20,21]. A total of 41 pathogenic *HEXB* mutations have been described [22].

GM2 activator deficiency or the GM2 AB variant, the final disease in the triad of β-hexosaminidase A deficiency disorders, was described in 1989 in an infant with the identical phenotype of TSD but normal *in-vitro* β-hexosaminidase A enzyme activity [23]. The disorder is caused by the absence of a third non-enzymatic protein, the GM2A protein or GM2 ganglioside activator. GM2A acts as a co-factor required for β-hexosaminidase A to exert the cleavage of the terminal *N*-acetyl galactosamine of GM2 ganglioside by binding membrane GM2 ganglioside molecules and presenting to the β-hexosaminidase A enzyme for degradation. The gene *GM2A* was cloned in 1989 [23–25] and seven mutations have been described as pathogenic [26]. Exceedingly rare, the GM2 activator deficiency has been reported only in the infantile form.

1. GM2 is a disease continuum

GM2 gangliosidoses present as a continuum of clinical phenotypes based on the amount of residual β-hexosaminidase A enzyme activity. Three clinical phenotypes have been described determined by age of onset as acute-infantile, sub-acute juvenile, and late-onset adult GM2 gangliosidoses (Figs. 1 & 2).

Of the three subtypes, acute infantile presents with negligible residual β-hexosaminidase A activity, thereby presenting with the most severe clinical signs and symptoms, including progressive weakness, excessive startle reaction, and characteristic cherry-red maculae. The infant may appear normal or mildly hypotonic at birth. At 6 to 8 months infants demonstrate plateauing and then loss of milestones with inability to sit or roll from side to side. By 18 months, seizures, myoclonic jerks and progressive macrocephaly resulting from reactive cerebral glial cell proliferation are common [27]. Loss of previously acquired skills, such as swallowing, combined with a severe deterioration in the second year of life typically leads to death between ages two and three [11,28]. With improved supportive care, including aggressive pulmonary toileting and gastrostomy tube placement, children with infantile GM2 are now surviving to age 5 to 7 years (Table 1). The neurologic symptoms and the rapid disease progression often can and have caused misdiagnoses including Canavan disease, infantile neuronal ceroid lipofuscinoses, infantile Alexanders disease, GM1 gangliosidosis type 1, mucolipidosis type II, sialidosis type 2, Gaucher disease type 2, and Niemann-Pick disease type A (Table 1) [11].

Juvenile GM2 gangliosidoses, the least common of the three subtypes, manifests with normal early development followed by a halt in acquisition of new skills by 3 to 5 years of age followed by loss of milestones and progressive decline. By the end of the first decade of life, children develop dysphagia, spasticity, and a decrease in visual acuity. Severe deterioration of motor skills including the inability to swallow and decerebrate posturing leads to death, usually by aspiration, in the second decade [11,28]. Rapidly progressive neurodegenerative disorders such as Gaucher disease type 3, GM1 gangliosidoses type 2, Canavan disease, sialidosis type II, infantile Alexander’s disease, ceroid lipofuscinoses, Juvenile Niemann-Pick C (NPC), and early-onset spinocerebellar ataxia, among others, should be considered in the differential diagnoses of juvenile GM2 gangliosidoses (Table 1) [11].

Late-onset Tay-Sachs (LOTS) and late-onset Sandhoff diseases (LOSD), collectively referred to as late-onset GM2 gangliosidoses, have symptoms emerging in the late teens and beyond. LOTS and LOSD have the most clinical variability in presentation and progression of all the GM2 gangliosidoses (Fig. 2) [11,28]. While LOTS and LOSD have been considered largely indistinguishable from each other on clinical grounds, some features, emerging from larger cohort observations, suggest that some aspects of the disease spectrum might be more prevalent in one form of the disease than in the other (Table 1) [29]. For example, psychosis presentation is rare in Sandhoff disease, while early sensory symptoms are rare in late-onset Tay-Sachs [29]. Early in the disease, conditions which could resemble late-onset GM2 gangliosidoses, may include spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), spinocerebellar ataxias (SCAs), Friedreich ataxia (FA), sialidosis

type I, spinal bulbar muscular atrophy (SBMA), adult NPC and primary psychiatric diagnoses (Table 1) [11,28,29].

Progressive neurogenic lower extremity weakness is perhaps the prototypical presentation of LOTS and LOSD. Weakness emerges from progressive loss of anterior horn cell motor neurons. Early in the presentation, weakness, fasciculations and muscle wasting selectively involves knee extensors (quadriceps) and hip flexor (iliopsoas) muscles leading to progressive difficulties climbing steps without use of handrails, jumping or raising from the sitting position without assistance of the upper extremities. As disease progresses, frequent falls develop because of inability to lock the knees firmly in extension during ambulation and stance. Injury and limited ambulatory capacity lead to use of assistive devices and eventually a motorized scooter or wheelchair. Weakness of the upper extremities emerges years later and disproportionally affects the triceps muscles. These symptoms and their progression appear indistinguishable between LOTS and LOSD (Fig. 3). In many cases, the anterior horn cell neuronopathy symptoms result in erroneous diagnosis of adult forms of spinal muscular atrophy including as SMA Type III (Kugelberg Welander disease), SMA Type IV, motor axonal neuropathies ALS and Kennedy's disease. Coexistence of cerebellar symptoms, dysarthria and vermian and subsequent pan-cerebellar atrophy would clearly favor a diagnosis of LOTS (Table 1).

Cerebellar dysfunction is considered an early finding in many adults with GM2 gangliosides. In fact, it is not uncommon to uncover cerebellar symptoms and imaging evidence of cerebellar atrophy at the time of LOTS's diagnosis regardless of the presenting symptoms. The combination of cerebellar signs and symptoms including mild dysmetria, eye movement abnormalities [30–32], cerebellar dysarthria [32–34], subtle long tract findings and lower extremity weakness may be easily mistaken for one of the spinocerebellar ataxias [35] (Table 1), In contrast to infantile GM2 gangliosidoses, the presence of a cherry red macula on fundoscopic exam of an adult with ataxia and myoclonus is highly suggestive of an alternate diagnosis of sialidosis type-I or galactosialidosis not LOTS or LOSD. Amongst symptoms related to cerebellar dysfunction, none seem as disabling as the progressive dysarthria of patients with LOTS including characteristic cerebellar features with unique superimposed fast pace, pressured, stuttering and/or explosive quality, that progressively impacts communicative abilities [32–34]. There is debate as to the degree to which cerebellar atrophy and cerebellar dysfunction, including dysarthria, might be more prevalent and severe in LOTS as compared to LOSD. These differences could result in cases with distinct cerebellar syndromes in LOTS and distinct neuromuscular phenotypes in LOSD [29,30,36].

Acute psychosis is a well-established presenting finding in some patients with LOTS. In fact, LOTS is one of the few neurometabolic disorders that presents with acute psychosis [34,37]. The psychiatric presentation may range from psychotic episodes [38], to bipolar depression requiring acute psychiatric care [32]. While most patients respond well to neuro-pharmacological treatment, achieving remission can be difficult in some and may require long term management [38]. Of note, some antipsychotic treatments have been reported to adversely affect the disease course of late-onset GM2 gangliosidoses [39–41] and should be avoided. Depression and anxiety are common comorbidities of late-onset

GM2 gangliosidoses across the disease course. Acute psychosis in the setting of LOSD is extremely rare or unreported.[29,42]. Retrospective developmental history review of patients with late-onset GM2 gangliosidoses and comparison to those of unaffected siblings or peers often uncovers subtle deficits emerging earlier in life. These include clumsiness, poor athletic abilities, mild tremor, or a nasal voice quality. These findings are subtle and often not brought to attention but point to an earlier phenotypic expression in late-onset GM2 gangliosidoses.

Other less common symptoms of early late-onset GM2 gangliosidoses may include spasticity, neuropathic sensory symptoms with dysautonomia and dystonia. Spasticity emerges from dysfunction of the upper motor neurons and their descending tracts (pyramidal tracts) causing increased muscle tone and exaggerated deep tendon reflexes. Upper motor neuron signs such as mild spasticity and exaggerated reflexes are often obscured by co-existing weakness but explain the common occurrence of pathological reflexes such as “crossed-adductor” and “extensor plantar” responses in some patients with LOTS and LOSD at early and moderate stages of their disease. Sensory symptoms and dysautonomia are reported to occur early in some patients with LOSD but are rarely or never a presenting symptom of for LOTS. Symptoms include distal painful burning, acroparesthesia worsened by heat and exercise, sensory loss, and overt dysautonomia from small diameter fiber sensory neuropathy [42–47]. Clinical and electrophysiological evidence of often asymptomatic peripheral neuropathy, elicited at the time of neurological examination (diminished sense to light touch, temperature or vibration) was present in 9/30 (27%) of patients with LOTS [48]. Dystonia represents abnormal involuntary muscle activity leading to abnormal repetitive movements and postures. Dystonia emerges from abnormal integration of sensorimotor signals from the basal ganglia, cerebellum, and thalamocortical networks. Dystonia may include dystonic hand and foot posturing, dystonic tremors and spasmodic dysphonia [32,49]. The latter adds a “breathy” or “strangled” voice quality with “overflow” overactivation of other facial and neck muscles on top of an already abnormal cerebellar dysarthria.

2. Pathogenesis of GM2 gangliosidoses

The neurodegenerative nature of GM2 gangliosidoses is evidenced by the progressive nature of disease-associated deficits, the progression of cranial MRI abnormalities and pathological findings in the CNS of affected patients. The low or absent β-hexosaminidase A enzyme activity resulting from absent or deficient *HEXA* or *HEXB* gene products (the α or β subunits of the β-hexosaminidase A enzyme), are unquestionably at the root of disease pathophysiology. Undigested GM2 ganglioside, an intermediate sphingolipid in the synthesis and degradation of higher brain gangliosides, accumulates in various tissues of the body but predominantly in the brain including neurons, microglia and neuroglia [35]. In neurons, it leads to the distinctive membranous cytoplasmic bodies (MCBs) (Fig. 1), zebra bodies and electron dense lipofuscin deposits [50,51] Cytoplasmic accumulation of these abnormal structures in patients’ brains and in animal models of GM2 gangliosidoses, give neurons their distinctive bloated appearance Fig. 1) [52]. Due to variations in age of onset and rate of progression, the extent and type of neuropathologic findings could differ [27]. For example, neuropathologic descriptions early-onset disease relate edema

and thickening of leptomeninges forming a meshwork of proliferating fibroblasts and macrophages and cortical atrophy that emerges in the first year of life. Neurons begin to lose their characteristic shape as cytoplasmic granules enlarge and proliferate with GM2 storage. Between 15 and 24 months, swelling of the white matter leads to compression of the lateral ventricles and brain weight begins to increase. Proliferation of macrophages and reactive astrocytes is associated with a decline in neurons numbers. By two years of age there is significant increase in brain size and swelling of cerebral hemispheres [27]. Accumulation of lipids in retinal ganglion cells contributes to the characteristic cherry red spot (Fig. 1) [27]. In late onset disease, the distribution and magnitude of accumulation might be sparce with anatomical structures such as the spinal cord and cerebellum appearing more impacted by the time of autopsy while other regions may be relatively spared [50,51].

3. Neurodegeneration in GM2 Gangliosidoses: A multipartite process

While the exact timing and sequence of events driving the very early stages of neurodegeneration remain unclear, GM2 accumulation in humans and in animal models seems uniformly associated with structural neuronal changes, vigorous microglial activation and proliferative response and neuroglial dysfunction. The cascading biochemical, cellular, and CNS-wide events throughout the disease process encompass many levels (Fig. 1). At its core, the blockade of enzymatic cleavage of GM2 ganglioside elicits downstream effects including functional and morphological disruption of intracellular organelles, deficient autophagy [53], abnormalities in lipid signaling and membrane homeostasis. These events not only affect neurons, but also microglia, astrocytes, and oligodendrocytes [54–57]. Activation of abnormal intracellular signaling cascades including pro-apoptotic signals [35,58] as well as dysregulated crosstalk amongst various cell lineages favors proinflammatory microglial activation [59,60]. Microglial activation and proliferation elicits waves of reactive astrocytes [61] which lose their ability to promote neuronal survival, outgrowth, synaptogenesis and phagocytosis, and rather, could induce neuronal and oligodendrocyte cell death [60–62]. In their totality, these events result in CNS-wide dysfunction with detrimental neurodevelopmental and neurodegenerative effects in early onset disease, and a predominantly neurodegenerative process in late disease. Depending the age of onset, disease burden has regional selectivity which determines the various phenotypic features of the disease [63,64 11].

The spectrum of molecular pathology; itself, a function of all possible biallelic combinations of known pathogenic “null” and “missense” alleles, is directly reflected in the degree of residual enzyme activity. Residual enzyme activity influences disease onset and to great extent, the slope of disease progression (Fig. 2). Time-dependent conditional gene expression experiments recapitulate some aspects of the human disease phenotype. [65]. It is important to consider that neurons, microglia, and oligodendrocytes alike, depend on lysosomal GM2 degradation “competence” in their normal function in processes that involve lipid signaling, membrane assembly, membrane recycling and housekeeping, axonal and dendritic sprouting, synaptic pruning, and axonal myelination. These events are critical not only during gestation and early life but also in the process of brain maturation, learning, adaptation, and housekeeping in normal and abnormal aging [66–69]

Microglial cells arise quite early during development from progenitors in the embryonic yolk sac. Microglial cells colonize the developing nervous system and persist in the adult brain [70]. While microglial cells closely resemble peripheral macrophages in their cellular properties and in their role as resident macrophages scavenging debris, surveilling for pathogens, etc., in their “unstimulated” state, microglia serve an important role in CNS development, angiogenesis, maturation and homeostasis [71]. The various cell markers and transcriptional profile of microglia can quickly switch from their “unstimulated” to a proinflammatory “stimulated” state [60]. This switch is accompanied by a multitude of events including ***a)*** rounds of replication (microglial proliferation), ***b)*** morphological changes from a radial appearance to ameboid (macrophage-like) cells armed with the capacity to release cytokines such as TNF alpha, transforming growth factor (TGF beta1), and interleukin 1 beta (IL1 beta) [60], ***c)*** express proinflammatory markers in the CNS (MHC class II, CD68, CD11b (CR3), 7/4, F4/80, nitrotyrosine, CD4 and CD), ***d)*** exert chemotaxis, ***e)*** perform antigen presentation to other proinflammatory cells [72] and **f)** disrupt blood–brain barrier permeability.

Contrary to the transcriptional profile typical of “unstimulated” microglia which quickly turns “off” after microglial stimulation, the high *HexB* transcriptional profile in “unstimulated” microglia remains elevated in ”stimulated” state, indicating that microglial GM2 competence is relevant across various stages of microglial function in animals [73]. Cortical tissue from patients with early-onset Tay–Sachs and Sandhoff diseases reveal transcriptional profiles consistent with microglia and astrocytes activation including expression of class II histo-compatability antigens, the pro-inflammatory cytokine osteopontin, and complement components, among others. [74]. These findings correlate well with other experimental studies in animal models [60]. Microglial proliferation serves to amplify and perpetuate inflammation. Inflammation itself threatens other cells types.[75] There is a well-choreographed interaction between microglia and oligodendrocytes and this interaction appears dysregulated in the models of GM2 gangliosidoses [72]. Abnormalities in myelin-associated lipids appear to precede other cellular events in the Sandhoff mouse model [54]. Disruption of oligodendrocytes impacts myelination during development and the activated microglial response can, in itself, promote demyelination [75] Deficient or disrupted axonal myelination by oligodendrocytes exerts detrimental effects on axon stability and contributes to axonal transection and retrograde neuronal degeneration [62].

Animal models have played a foundational role in understanding the pathogenesis of GM2 gangliosidoses and have helped conceptualize and develop therapies [76]. For example, Wada et. al.’s work on symptomatic Sandhoff mice also demonstrated an early and robust apoptotic neuronal signature in the caudal regions of the brain and spinal cord as well as a prominent microglial activation response and some of this response is ameliorated by bone marrow transplantation (BMT) [77]. Production of Tay-Sachs mouse models via targeted interruption of *HexA* gene in embryonic stem cell have shown characteristic biochemical and neuropathologic features of Tay-Sachs disease. These features included loss of β-hexosaminidase A activity and collection of GM2 ganglioside seen in characteristic MCBs in an age-dependent manner [78,79], However, these animals, lack the prototypical early severe phenotype of infantile β-hexosaminidase A deficiency [80,81]. This difference

between the *HexB* (Sandhoff) and *HexA* (Tay-Sachs) deficient mouse models is explained by the capacity of HexA deficient mice to catabolize stored GM2 ganglioside using sialidase(s) to remove sialic acid and form the glycolipid GA2, which is further processed by β-hexosaminidase B [80,82,83]. By creating a doubly null (*HexA*$^{-/-}$*Neu3*$^{-/-}$) mouse, the severe disease aspects of infantile Tay-Sachs are much better recapitulated, serving as suitable model for preclinical studies of severe Tay-Sachs [84].

How various cell linages interact and contribute to neurodegeneration are of great interest to understanding the disease process and to uncovering potential therapeutic opportunities. Histological and gene expression analysis revealed that an abnormal upregulation of microglial activation preceded neuronal cell death. Mutant mice treated by bone marrow transplantation in an attempt to repopulate with competent microglia suppressed the explosive activation of microglia and slowed neuronal cell death [77]. In a mouse model of Sandhoff disease, stimulation of the immune receptor FcRγ has been established as a contributor to the development of astrogliosis during the early phase of the disease and it suggests that agents targeting this receptor could offer therapeutic opportunities in GM2 gangliosidoses [85].

While the effects of β-hexosaminidase A deficiency in development and subsequent disease progression are not fully understood [61], human cerebral organoids derived from induced pluripotent stem cells (iPSCs) have been a useful avenue to study changes in neural differentiation. Cerebral organoids modeling neural differentiation in infantile Sandhoff disease depicted an increase in GM2 ganglioside accumulation, enlarged volume of the organoids themselves when compared to control organoids, increased cellular proliferation, and impaired neuronal differentiation [86]. Neurodevelopmental alterations are also recapitulated in the GM2 gangliosidoses zebrafish model showing increased lysosomal speckles in radial glia, reduced locomotor activity, and increased apoptosis [35]. The dynamics of normal cortical pyramidal cell dendritogenesis is disrupted in models of GM2 gangliosidoses resulting in morphological disruption at the axon hillock (mega neurites) and formation of ectopic synaptic spines [87,88]. Cortical layer organization in the mouse model of Sandhoff disease is abnormal [89].

4. Neurodegeneration in early vs. Late-onset disease

Comparison of symptoms and clinical course of early versus late-onset GM2 gangliosidoses, highlights important differences (Figs. 1 & 2) (Table 1). In early disease, complete or nearly complete absence of lysosomal GM2 turnover is predicted. Developmental processes heavily dependent on lipid signaling, membrane assembly and turnover such as axon elongation and sprouting, myelination, migration, and synaptic pruning are likely impaired. Cellular dysfunction affects neurons, microglia and oligodendrocytes imparting a neuro-developmental dimension to early GM2 gangliosidoses. Clinical findings in early disease such as truncal hypotonia, cherry red macula, seizures, myoclonus and early developmental arrest followed by rapid loss of early milestones argues for a disease process of rapid progression that diffusely burdens the white matter of the cerebral hemispheres, cortex and retina [11]. This line of reasoning is well supported by findings in infantile GM2 that include swollen and abnormal white matter on MRI [90] leading to macrocephaly,

massive glial proliferation, excess accumulation of GM2 ganglioside and substrate storage particularly in retinal ganglion cells. On the other hand, patients with late-onset GM2 gangliosides, most often develop normally and most live productive lives prior to symptom onset. Their disease is characterized by slow progressive accumulation of disabilities that share many features common to other neurodegenerative processes including neuromuscular conditions such as spinal muscular atrophy (SMA) or amyotrophic lateral sclerosis (ALS), or progressive cerebellar syndromes akin to spinal cerebellar ataxias (SCAs) [11,29,91]. Abnormal myelination is not a feature of late-onset disease [92]. Residual enzyme activity may be sufficient to allow for normal development and myelination into adulthood, but, as time progresses, perhaps, the burden of substrate accumulation or other yet unknown factors reach a critical “threshold” where scales tip towards symptom onset and progression (Figs. 1 & 2). This clinical “threshold” may be driven by the interplay of residual enzyme activity in the various cell types, age-related neuronal and synaptic attrition, and environmental factors on a genomic and epigenomic background; conceptually similar to other neurodegenerative disorders such as Parkinson’s disease, sporadic ALS or Alzheimer’s disease [93]. Processes that are known to be involved in other forms of neurodegeneration such as beta amyloid clearance, progranulin function, and alpha synuclein metabolism variously intersect with abnormalities uncovered in disease models of GM2 gangliosidoses [57,94,95]. Neurodegeneration in late-onset GM2 gangliosidoses has parallels to neurodegeneration in other LSDs (Gaucher’s disease, NPC, ceroid lipofuscinoses, etc.) and in how it converges into pathways involved in more common neurodegenerative conditions [96–99].

5. Symptom progression in Late-onset GM2 gangliosidoses

Patients with late-onset GM2 gangliosidoses demonstrate a substantial burden of disease in the spinal cord anterior horn cells and the cerebellum, indicating that these structures have a heightened vulnerability in the setting of late-onset GM2 gangliosidoses. A substantial proportion of late-onset disease symptom burden and its progression is driven by dysfunction in these two regions (Figs. 3 and 4) [11,93].

Progressive anterior horn motor neuron loss (anterior horn cell neuronopathy) drives progression of the neurogenic weakness and muscle atrophy characteristic of LOTS and LOSD [29,34,100]. A clear determinant for the predilection for an earlier and more severe involvement of the quadriceps and iliopsoas in the lower extremities and the triceps muscles in the upper extremities is lacking. It is interesting to note, however, these muscles are active in antigravity and pelvic girdle stabilization and postures, particularly during crawling or in our primate ancestors, during quadrupedal stance [101]. Antigravity motor neurons pools in the spinal cord have anatomical and functional characteristics that differentiate them from other motor neuron pools. Motor neurons differentiate and aggregate in neuron pools according to target muscles and this differentiation occurs according to a developmental program orchestrated in time and space by a complex combination of transcriptional signals [102]. Antigravity motor neurons exhibit sustained “tonic” action potential firing pattern and their activity modulation is influenced by descending inputs that differ from those of motor neurons with “phasic” activation patterns, but how GM2 renders certain populations of motor neurons more susceptible to degeneration than others is unclear.

Models of other lower motor neuron (LMN) degeneration including *Sod1* and *Optn* deficient mouse models of ALS demonstrate the interplay between microglia and oligodendrocytes influencing LMN cell survival at the spinal cord level [103]. Microglial proliferation, cytokine release, and activation of receptors such as RIPK1 are a critical component of cell death in neurodegeneration [103–105]. “Cross-talk” between activated microglia and oligodendrocytes results in subclasses of microglia that are directly involved in neurodegeneration, loss of myelin coverings and subsequent retrograde degeneration of anterior horn cells [104]. Similar processes are likely implicated in GM2 gangliosidoses [84].

Anterior horn motor neurons and Purkinje cells share in their exuberant morphological features resulting in a large surface (membrane) area when compared to other neuronal populations. Anterior horn cells have cylindrical axon extensions into peripheral motor nerves which, in an adult human, could be well over one meter long. Purkinje cells, on the other hand, have a large dendritic tree which has rapidly accelerated in complexity during the evolutionary transition from non-human primate to humans [106]. This evolutionary acceleration in complexity is recapitulated ontogenically in the rapid increase in Purkinje cell dendritic complexity during fetal development and infancy [107]. The resulting exuberant dendritic tree confers to Purkinje cells a surface area that is several orders of magnitude larger than any other neuronal cell type [108,109]. The cerebellum is highly cellular and may contain over four times more neurons than the neocortex [110]. It is estimated that the human cerebellum, despite its relative smaller size, has almost 80% of the surface area of the entire neocortex resulting from highly compact folding of the folia [111]. While highly cellular, the functional connectivity of the cerebellum is modular with an astonishing convergence (integration) of inputs onto Purkinje cells. Inputs from many brain regions arrive to the cerebellum. Tens of thousands of synaptic inputs may coverage into any given Purkinje cell’s dendritic tree. Purkinje cell axons provide the sole output of the cerebellum via connections to the deep cerebellar nuclei. Second order connections to relay structures such as the thalamus, creates a system of widespread reciprocal interconnected networks [112].

Imaging findings in LOTS patients demonstrates prominent cerebellar atrophy at the time of diagnosis [29,30,92], and indeed, progression of atrophy is demonstrated thru the course of the disease (Fig. 4A). Cranial imaging across the disease span suggests that cerebellar atrophy progresses out of proportion to other anatomical brain structures [29,36]. Neuropathology studies of the cerebellum in LOTS shows loss of Purkinje cells and advanced stages of cerebellar atrophy and degeneration [51].

Purkinje cells are uniquely vulnerable to injury and are frequently the first target of noxious events including neurotoxic exposures (ethanol, some anti-epileptic agents, chemotherapy, etc.), hyperthermia, anoxia, and metabolic, inflammatory, immune mediated and many genetic disorders such as NPC and many repeat expansion disorders which have ataxia as an earlier manifestation [58,113–115]. The turnover and remodeling of dendritic spines of Purkinje cells is an important aspect of neuronal plasticity required for development, learning and adaptation [116,117]. These processes have been widely implicated in disorders such as autism [118,119] and psychiatric illness [120,121]. Dendritic sprouting, pruning

and membrane maintenance are metabolically expensive as demonstrated by the effects caused by dysfunctional mitochondrial fission and migration onto dendritic arborizations of Purkinje cells and the role of accumulating reactive oxygen species contributes to cerebellar degeneration [122]. While the exact metabolic “cost” required to preserve normal membrane homeostasis, lipid recycling (including GM2), resting membrane potentials and other basic housekeeping functions of Purkinje cells and anterior horn cells is unknown; it is likely to be substantial and to contribute to neurodegeneration [123–126]. Lysosomal GM2-incompetence in Purkinje, anterior horn cells and in the large cadre of related support cells represent a system vulnerability capable of engaging known pathways of Purkinje cell degeneration [126].

In the last two decades clinical and human functional neuroimaging studies of cognition have discovered a surprising involvement of the cerebellum for activities well beyond those associated with motor control [127]. Anatomically, the cerebellum is well position to reciprocally communicate broadly with other brain regions including cortical motor sensory areas and multiple nonmotor areas in the prefrontal and posterior parietal cortex (Fig. 4B). Thus, the closed-loop arrangement provides a network basis for neocortical-cerebellar interactions and the anatomical substrate to influence not only the control of movement but also many other aspects of human development, cognition and behavior [128]. The concept of the cerebellar cognitive affective syndrome (CCAS) has become a well-defined entity that captures the neuropsychological profiles and deficits that emerge in the context of cerebellar pathology [129] (Fig. 4 B and C) (modified from [112]) and involve neocortical areas engaged in complex cognitive processes, such as attention, executive function, language processing, learning etc. Aside from neuromuscular weakness (emerging from spinal cord pathology), dysfunction of large scale networks through the cerebellum may account for many clinical and behavioral aspects of late-onset GM2 gangliosidoses such as incoordination, tremor, executive dysfunction [30,91], impaired eye movements [30,31], dysarthria and conceivably some aspects of the psychiatric symptoms [32].

6. Therapeutic possibilities

Therapy in the GM2 disorders will require mitigation and/or reversal of stored GM2 ganglioside in disease-relevant tissues. Minimizing the diagnostic odyssey through newborn screening and community and physician education will be keys to successful therapy, particularly in the rapidly progressive infantile onset disease. Early diagnosis will also be critical in juvenile and adult-onset forms where considerable compromise of the CNS takes place before symptom onset and subsequent diagnosis. However, even initiating treatment in the first few weeks of life may not be sufficient to reverse the storage and/or the consequences of storage that have been present since mid-gestation in infantile onset patients [130,131]. Trials in juvenile and late-onset disease are confounded by small patient numbers (juvenile) and the variability in symptom onset and progression (juvenile and late-onset) and may require novel or more lengthy trial designs to demonstrate a positive outcome.

Mitigation of GM2 storage can theoretically be accomplished by reducing GM2 substrate accumulation, increasing β-hexoaminidase A enzyme activity, or a combination of the two.

Small molecules such as miglustat, eliglustat, and more recently venglustat, all competitive inhibitors of glucosylceramide synthase, the first committed step in glycosphingolipid synthesis, have been used with variable effect. Miglustat was shown to be successful in extending the lifespan of the Sandhoff mouse model by 40%, from 125 to 170 days [132] yet miglustat in a human clinical trial did not achieve its proposed endpoint of increase in manual muscle strength at the 12 and 36 month timepoints [133] although there was some indication that the dysarthria was improved in some adult-onset patients. Unacceptable side effects such as diarrhea and flatulence caused early withdrawal of some subjects from the study. Eliglustat has been effective in treating type 1 Gaucher disease [134–137] and is now FDA approved for this indication, but it has poor CNS penetration for neuronopathic forms of the disease. Venglustat has improved CNS penetration and is currently in clinical trials for LOTS and LOSD (NCT04221451), type 3 Gaucher disease (NCT02843035), and Fabry disease (NCT02228460). NCT04221451 also has a small open-label arm to treat other disorders including patients with juvenile onset GM1 or GM2 gangliosidoses.

Small molecule therapy extends beyond substrate reduction and utilizes strategies to screen approved drugs for repurposing. Pyrimethamine is one such drug that showed the ability to decrease GM2 storage [138]. A second drug, *N*-acetyl leucine, originally approved for the treatment of motion sickness has recently been shown to improve lifespan in murine models NPC and SD and in patients with NPC, TSD, and SD [139]. Multi-center open-label trials of *N*-acetyl-L-leucine for NPC (NCT03759639), GM2 gangliosidoses (NCT03759665) and ataxia telangiectasia (NCT 03759678) are currently underway.

Reasoning that microglia are macrophage derived, Norflus et al demonstrated an increase in survival from 4.5 months to 8 months and improvements in behavioral testing in the Sandhoff disease mouse receiving bone marrow transplantation at 10–16 days of age [140]. Treating with a combination of BMT and miglustat further improved survival [141]. In a similar effort, three of five children with infantile Tay-Sachs disease undergoing umbilical cord blood transplant survived greater than 5 years but the quality of life was severely limited [142]. Bone marrow transplant (BMT) did not impact disease progression in a patient with juvenile Tay-Sachs disease when compared with her older untreated sibling [143], though, on a single case report, BMT was reported to slow neurodegeneration in patients with LOTS [138,144]

Enzyme replacement therapy (ERT) [1] is widely available for many LSDs including Gaucher, Fabry, and Pompe diseases and several mucopolysaccharidoses. ERT for GM2 gangliosdiosis was first attempted by Johnson who delivered β-hexosaminidase A intravenously to a child with Sandhoff disease. Although enzyme was detected in the liver at autopsy it was not found in the CSF or brain parenchyma presumably because enzyme was not able to cross the blood brain barrier (BBB) [145]. Highly phosphomannosylated β-hexosaminidase A enzyme delivered intraventricularly to Sandhoff disease mice restored enzyme activity in neurons, reduced GM2 and GA2 substrates and resulted in modest improvement in behavior and longevity [146]. More recently, a genetically engineered HEXB enzyme encoding the chimeric human β-subunit containing partial amino acid sequence of the α-subunit by structure-based homology was injected into the cerebral ventricles of Sandhoff disease mice restoring β-hexosaminidase A activity in the brains

and reducing GM2 ganglioside storage in brain parenchyma. The authors suggest that this re-engineered HexB protein might be less antigenic in Tay-Sachs disease patients with null mutations in the HexA gene [147]. The delivery of fusion proteins comprised of β-hexosaminidase A enzyme coupled with ferritin or other proteins containing receptors on the surface of brain endothelial cells have also been proposed as strategies to traverse the BBB, but none have progressed to clinical trials.

Gene therapy provides an attractive option for therapy for LSDs including GM2 disease since cross correction by secretion of enzyme and uptake by neighboring cells implies that not all cells need to be transfected to provide widespread enzyme distribution [148]. Effective gene therapy for GM2 disease was demonstrated first in the Sandhoff mouse model [149,150] using intracranial injection of AAV2 vectors containing the sequence for the human alpha (*HEXA*) and beta (*HEXB*) subunits of β-hexosaminidase A enzyme. Lifespan and function were extended from 4 months to greater than 1 year in treated animals. These encouraging results were extended to the feline Sandhoff model where intracranial injection of AAVrh8 vectors containing alpha and beta subunits corrected GM2 storage and resulted in improved survival [151–154] even when administered to symptomatic animals, a similar correlate to human patients at the time of diagnosis [155]. Utilizing a brain size more commensurate with that of a young child, Gray-Edwards and colleagues [156] demonstrated therapeutic efficacy using intracranial injection in a Tay-Sachs sheep with AAVrh8 vectors containing the alpha and beta subunits. This intracranial injection of equimolar concentrations of AAV vectors containing the alpha and beta subunits has recently been advanced to clinical trials for patients with infantile and juvenile TSD and SD (NCT04669535). Improvements in vector design to accommodate alpha and beta subunits in the same AAV vector [157] and safe and reliable vector delivery [158] have also been demonstrated. A similar, bicistronic AAV9 vector containing both *HEXA* and *HEXB* has recently been approved for a phase 1 trial in infantile GM2 patients (NCT04798235).

To alleviate the need for delivery of both *HEXA* and *HEXB* genes, a modified α-subunit containing critical sequences from the β-subunit was used to create a homodimer (Hex M) [159] that was able to degrade GM2 substrate. This AAV-based vector injected into neonatal SD mice was able to extend the lifespan and improve behavior [160]. As a first demonstration of the potential for genetic manipulations in the treatment of GM2 gangliosidoses, AAV8 carrying the HexM construct was also used in combination with a second vector carrying the CRISPR Cas9 gene editing construct for integration into the albumin locus. Neonatally injected SD mice examined at 4 months showed increased enzyme activity in all tissues examined, including brain, and improved performance on rotarod analysis [161].

Intravenous administration and targeted delivery of AAVs selective for brain endothelial receptors and containing *HEXA* and *HEXB* have also been shown to reduce ganglioside accumulation and improve survival and motor function in SD mice [162].

Progress using gene therapy has not been limited to in vivo delivery of AAV vectors. A novel lentiviral vector containing both *HEXA* and *HEXB* genes successfully transduced SD mouse neurons and glial cells as well as bone marrow-derived hematopoietic stem/

progenitor cells and human SD fibroblasts [163]. A similar *HEXA/HEXB* lentiviral vector has recently been used to transduce hematopoietic stem cells from a humanized SD mouse model for *ex vivo* delivery. The engrafted mice showed improvements in both motor and behavioral skills [164].

Approval of specific therapies for the GM2 gangliosidoses will require not only improvement in relevant biomarkers of disease progression, but in outcomes that demonstrate meaningful clinical improvements in the quality of life for patients and their families. Optimizing supportive care with physical, occupational and speech/language therapies will be equally important. A multiprong approach combining therapies that reduce substrate synthesis, improve or restore β-hexosaminidase A activity against stored GM2 while mitigating inflammation/neurodegeneration may be required to obtain consistently improved lasting outcomes.

7. Conclusions

The last three decades have provided a much better understanding of GM2 gangliosidoses. Cloning and sequencing of the genes for *HEXA* and *HEXB* allowed recognition of common mutations, which combined with enzyme testing has offered the possibility of carrier testing for at risk populations, prenatal testing, and more rapid and accurate patient diagnosis. The development of animal models of GM2 gangliosidoses has provided platforms to understand the biology of β-hexosaminidase A, the effects of GM2 accumulation on the nervous system and the cascade of events that unfolds as the disease process evolves in time and space, including complex neurodevelopmental, neuroinflammatory and neurodegenerative aspects involving not only neurons but also microglia, oligodendrocytes and astrocytes [76,165]. Cell and animal-based models have provided the opportunity to test a variety of therapeutic strategies, most recently, in vivo delivery of viral vectors containing both *HEXA* and *HEXB*. Translation of these efforts to patients suffering from GM2 gangliosidoses are currently being sought.

While we divide GM2 gangliosidoses in subgroups, it is very clear that GM2 gangliosidoses represents a disease continuum driven by the amount of residual β-hexosaminidase A activity. At the extremes of this disease spectrum, early and late onset GM2 gangliosidoses, the patient-experience is quite different. Despite sharing a common mechanism (β-hexosaminidase A enzyme deficiency), the time of symptoms onset, slope of progression, distribution of pathology and mechanisms leading to neuronal dysfunction may vary. Early disease may have a neurodevelopmental and dysmyelination aspects followed by neuroinflammatory and rapidly progressing neurodegenerative processes that burden the hemispheres, cortex, white matter, and retina; while late-onset disease has neuroinflammatory and neurodegenerative features that disproportionally burden the spinal cord anterior horn cells and the cerebellum and may share features more common to other age-related neurodegenerative diseases. The latter creates a challenge for early diagnosis as many patients may easily be mistaken for common forms of adult neurodegeneration such as ALS or spinal cerebellar ataxias. While the clinical course of GM2 gangliosidoses emerging from *HEXA* or *HEXB* mutations have been largely considered indistinguishable from each

other in early disease (Table 1), in late-onset disease, some features may be more prevalent in one form than the other.

As potential disease modifying therapies, including gene therapy emerge, their success (alone or in combination) are likely to be dependent on disease burden and preexisting pathology at the time of therapy initiation. The definition of successful outcome(s) will require careful consideration of the age of symptom onset, disability, slope of progression, targeted tissues, and targeted symptoms, all variable across the disease spectrum. A concerted educational effort should be in place for early recognition of GM2 gangliosides across all age groups, but particularly in adults with late-onset disease, since the success of therapy may be measured in the long-term preservation of function. Currently, time from symptom onset to a molecular diagnosis of late-onset GM2 gangliosidoses is unacceptably protracted with many patients being diagnosed at advanced stages of disability.

Acknowledgements

The authors wish to thank and acknowledge all patients and families that have participated in the Natural History of Glycosphingolipid and Glycoprotein Lysosomal Storage Disorders (NCT0002996) at the National Institutes of Health (NIH) in Bethesda, MD. We also wish to acknowledge the National Tay-Sacks & Allied Diseases Association (NTSAD) for their enduring dedication and support to patients and families with GM2 gangliosidoses and related disorders and the Katie and Allie Buryk Research Fund for supporting increased multidisciplinary scientific collaboration on GM2 gangliosidoses. The authors thank Dr. Rick Proia for his comments, suggestions, and critical review of this manuscript.

This work is supported by funds from the NIH Intramural Research Program (IRP) to the National Human Genome Research Institute (NHGRI) and funding from the Office of the Director's Common Fund to the Undiagnosed Diseases Program/Undiagnosed Diseases Network.

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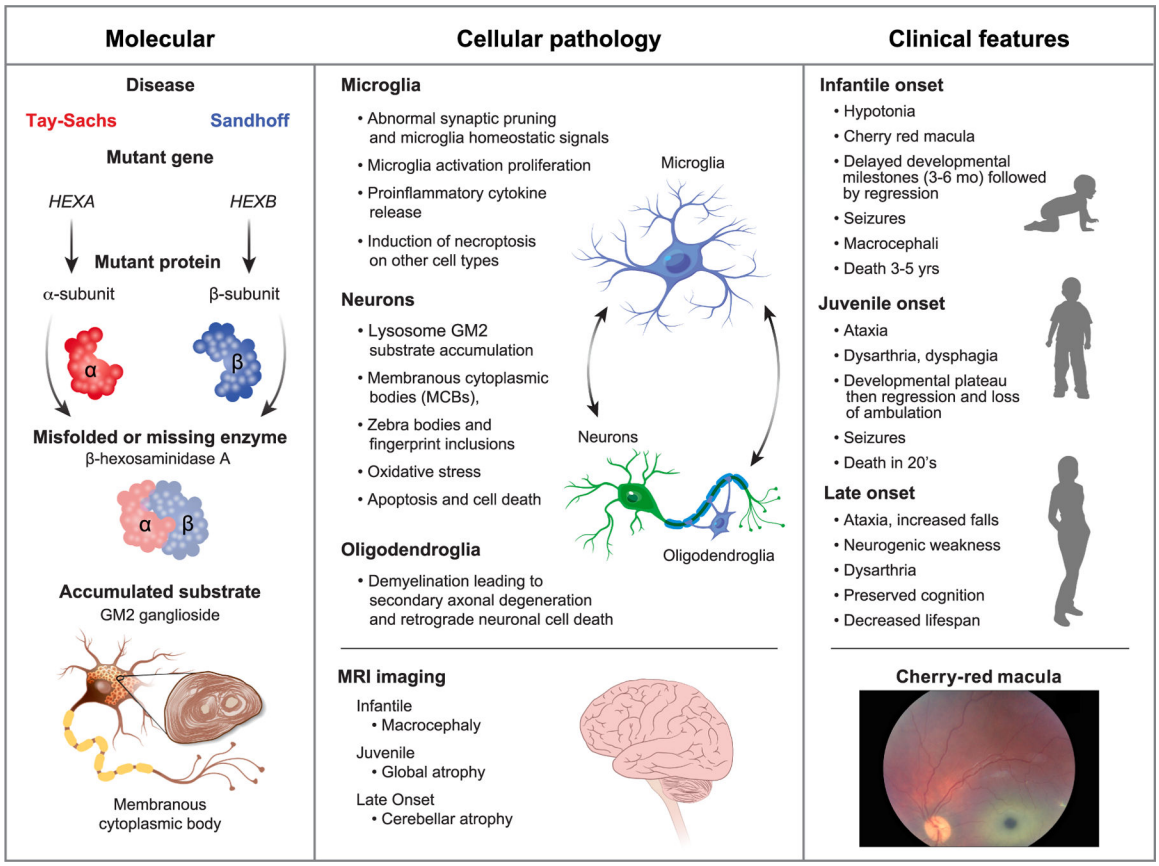

Fig. 1.

Schematic representation of the GM2 gangliosidoses. β-Hexosaminidase A deficiency emerges from biallelic null or missense mutations in the genes *HEXA* (Tay-Sachs) or *HEXB* (Sandhoff) disease, coding the alpha or beta subunits of the enzyme. β-hexosaminidase A is the only configuration of this dimeric enzyme capable of degrading GM2 substrate. Its deficiency renders neurons and other cells in the nervous system unable to degrade GM2 gangliosides at the lysosomal level leading to substrate accumulation exemplified by membranous cytoplasmic bodies visible on ultrastructural studies (**Left**). GM2 gangliosidoses involve dysfunction on multiple cell types including neurons, microglia and oligodendrocytes ultimately resulting in neurodegeneration (**Center**). Residual enzyme activity determines disease onset, symptoms and progression which has led to the categorization into disease subtypes (infantile, juvenile, or late onset) GM2 gangliosidoses (**Right**). A cherry-red spot is a characteristic ophthalmological feature of infantile GM2 gangliosidosis. A yellowish tint emerges from accumulated substrate in the macular region of the retina that contrasts with the darker appearing foveal center (**Bottom Right**).

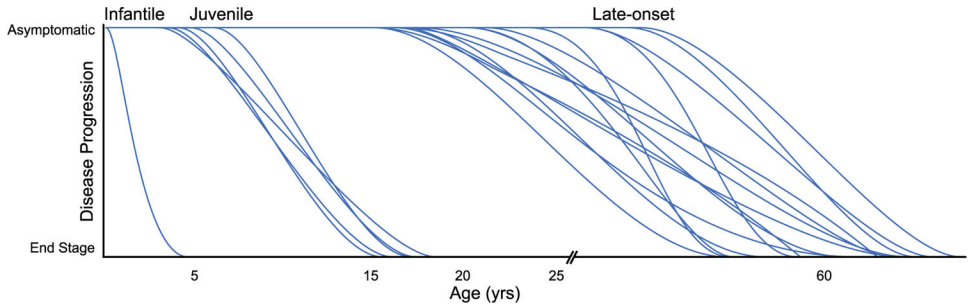

Fig. 2.

Natural history of three forms of GM2 gangliosidoses (Infantile, juvenile and adult or Late-onset) disease. Note the differences in age and slope of progression for the three forms. Progression is more homogeneous and steeper in earlier disease but more variable and shallower in late-onset disease. Ultimately, disease onset is a function of residual enzyme activity with early onset disease having complete or nearly complete absence of β-hexosaminidase A enzymatic activity.

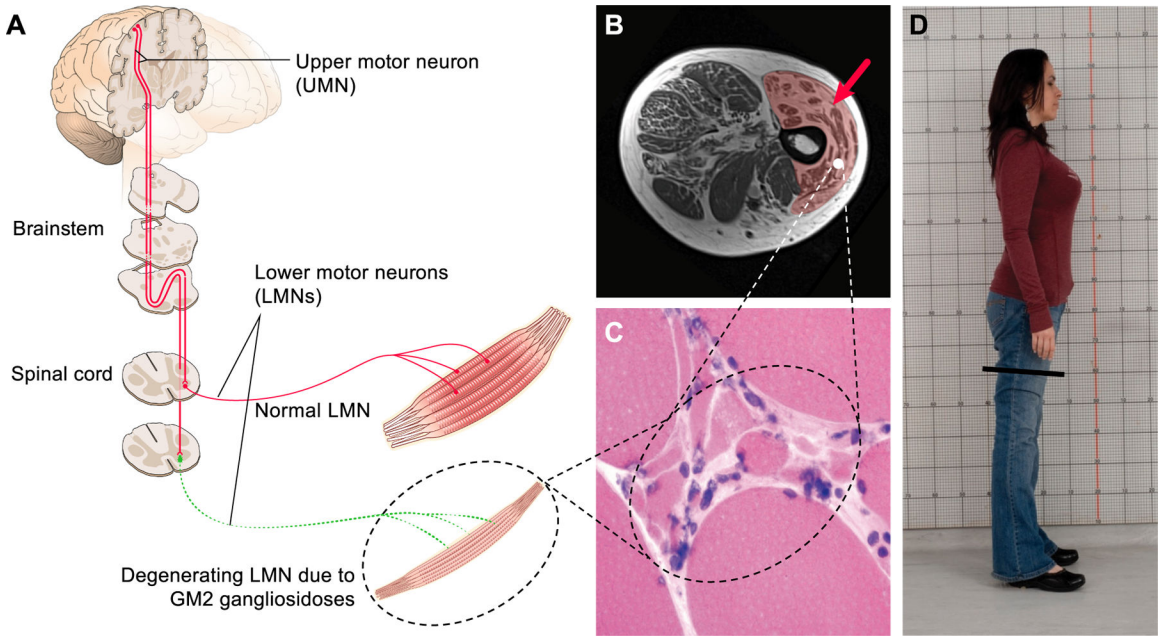

Fig. 3.

Schematic representation of the progressive lower motor neuronopathy characteristic of late-onset GM2 gangliosidoses. Degeneration of anterior horn cells (lower motor neurons) due to late-onset Tay Sachs or Sandhoff disease leads to denervation and neurogenic muscle weakness **(A)**. Muscle atrophy in is particularly severe in the quadriceps muscles (red arrow and highlighted muscle on thigh MRI) when compared to muscles on the posterior compartment of the thigh. On routine histology, bundles of degenerating fibers (enclosed in dashed oval) containing smaller angular fibers represent muscle fibers undergoing degenerating due to loss of their innervating anterior horn cell prototypical of neurogenic atrophy due to anterior horn cell neuronopathy (**B & C**). Hyperextension and “locking” of the knees to achieve antigravity support is characteristic of the stance and ambulation of patients with LOTS and LOSD experiencing quadriceps weakness (knee extension weakness). This finding is often accompanied by increased lumbar lordosis (**D**).

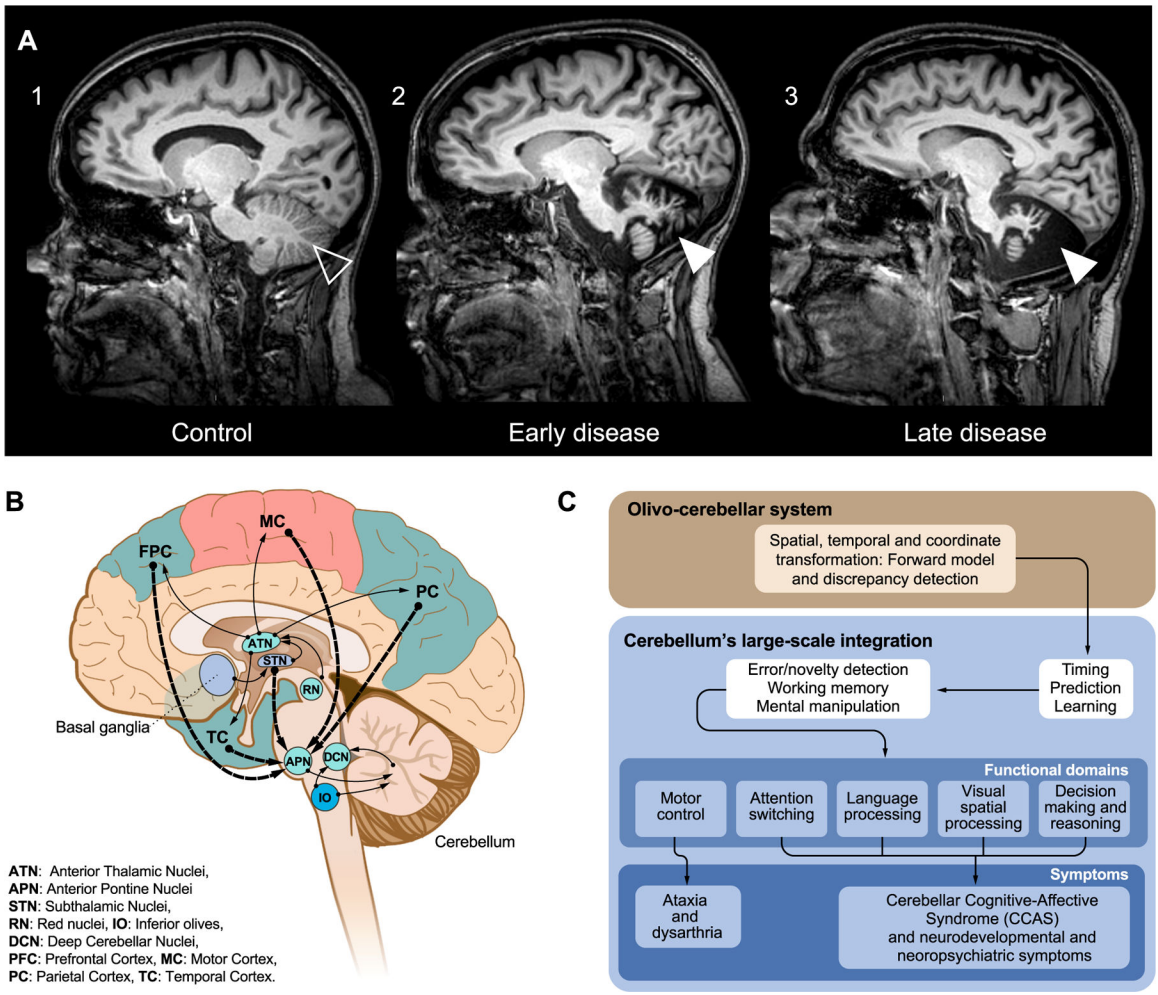

Fig. 4.

Panel A. Cranial T1 weighted sagittal MRI images over the right middle cerebellar peduncle in a healthy control (1), individual at the time of late-onset Tay Sachs diagnosis (2) and individual in an advanced state of late-onset Tay Sachs (3). Arrow heads point to the posterior fossa region normally occupied by the cerebellum. Images illustrate selective progressive cortical atrophy out of proportion to atrophy of other brain regions in patients with GM2 gangliosidoses (solid arrowheads) compared to a normal control subject (open arrowhead). **Panel B**. Large scale distributed cortico-cerebellar loops provide the neural substrate for the cerebellum to influence complex behaviors besides motor control in health and diseases including late-onset GM2 gangliosidoses. All cerebellar outputs originates from Purkinje cell connections to deep cerebellar nuclei including the dentate nuclei (DCN). In turn these nuclei have broad projections to the cortex and other CNS regions (solid arrows). Reciprocal cortical projections (dashed arrows) to the anterior pontine nuclei (APN) provide the basis for cerebellar input with robust convergence of many inputs into Purkinje cells which are particularly vulnerable to injury, including accumulation of GM2 ganglioside. **Panel C.** Schematic representation of the many aspects of behavior (beyond motor control) impacted by the function of the cerebellum and how cerebellar dysfunction could lead to not only to ataxia but also to the cerebellar cognitive affective syndrome (CCAS) which likely

contributes to cognitive and affective symptoms of late-onset GM2 gangliosidoses. (**B** and **C** are modified from D'Angelo & Casali, 2012 [112]).

Table 1

Clinical Findings and Differential Diagnosis in GM2 Gangliosidoses [11,28,29].

	Infantile GM2 Gangliosidoses	**Juvenile GM2 Gangliosidoses**	**Late-onset GM2 Gangliosidoses**
Key Presenting Findings	Presentation starting at age 3–6 months: - Progressive weakness - Exaggerated startle response - Decreased visual attentiveness and characteristic cherry-red macula	Presentation starting at age 2–5 years: - Abnormal gait - Dysarthria - Loss of previously acquired skills and cognitive decline	Presentation starting in late teenage years[a]: - Lower extremity weakness affecting quadriceps muscles and hip flexor muscles - Cerebellar findings • Dysarthria and incoordination[b] • Cerebellar atrophy - Acute psychosis[b] - Mild spasticity and/or dystonia - Sensory symptoms and dysautonomia[c]
Disease Progression	Rapid progression starting at age 8–10 months: - Loss of previously acquired skills - Rapid deterioration of vision - Enlargement of head and ventriculomegaly - Seizures and myoclonic jerks - Difficulty swallowing - Decerebrate posturing - Death between 2 and 3 years	Moderate Progression: - Spasticity - Dysphagia - Seizures - Decrease in visual acuity - Rare observation of cherry-red macula - Vegetative state with decerebrate posturing by age of 10–15 years	Slow progression: - Progressive neurogenic weakness and wasting with muscle atrophy, cramps, and fasciculation - Knee extensor/hip flexion muscle weakness progressing to the upper extremities (triceps predominant) Dysarthria with cerebellar features. May have superimposed spasmodic dysphonia, stuttering and explosive and pressured quality[b] - Decreased balance and dexterity - Saccadic dysmetria and abnormal saccadic gain - Psychiatric manifestations may include acute psychosis, depression, anxiety, and mania[b] - Deficit in memory and executive function
Differential Diagnosis	Canavan disease Neuronal ceroid lipofuscinoses Galactosialidosis Krabbe disease Gaucher disease type 2 Alexander disease, infantile form GM1 gangliosidosis type 1 Mucolipidosis II Sialidosis type II Niemann-Pick disease type A	Canavan disease Ceroid Lipofuscinoses Galactosialidosis Juvenile Niemann-Pick Gaucher disease type 3 GM1 gangliosidosis type II Spinocerebellar ataxia	Spinal muscular atrophy (SMA) Amyotrophic lateral sclerosis (ALS) Spinocerebellar ataxias (SCAs) Friedreich ataxia (FA) Primary psychiatric diagnosis Sialidosis type I Spinal bulbar muscular atrophy (SBMA) Adult Niemann-Pick (NPC) Axonal motor and sensory neuropathies

Key clinical findings at presentation, features of disease progression for the three subtypes of GM2 Gangliosidoses (**Top**) and differential diagnostic considerations (**Bottom**). Some features of late-onset disease might be more prevalent in Tay-Sachs than Sandhoff disease.

[a] In retrospect, many families of patients diagnosed with late-onset GM2 gangliosidoses may report earlier subtle issues including clumsiness, mild tremor, poor athletic abilities, and/or dysarthria.

[b] More common in Tay-Sachs.

[c] More common in Sandhoff disease.