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Minireview

Types A and B Niemann-Pick disease

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ABSTRACT

The eponym Niemann-Pick disease (NPD) refers to a group of patients who present with varying degrees of lipid storage and foam cell infiltration in tissues, as well as overlapping clinical features including hepatosplenomegaly, pulmonary insufficiency and/or central nervous system (CNS) involvement. Due to the pioneering work of Roscoe Brady and co-workers, we now know that there are two distinct metabolic abnormalities that account for NPD. The first is due to the deficient activity of the enzyme acid sphingomyelinase (ASM; "types A & B" NPD), and the second is due to defective function in cholesterol transport ("type C" NPD). Herein only types A and B NPD will be discussed. Type A NPD patients exhibit hepatosplenomegaly in infancy and profound CNS involvement. They rarely survive beyond 2–3 years of age. Type B patients also have hepatosplenomegaly and pathologic alterations of their lungs, but there are usually no CNS signs. The age of onset and rate of disease progression varies greatly among type B patients, and they frequently live into adulthood. Intermediate patients also have been reported with mild to moderate neurological findings. All patients with types A and B NPD have mutations in the gene encoding ASM (*SMPD1*), and thus the disease is more accurately referred to as ASM deficiency (ASMD). Herein we will review the clinical, pathological, biochemical, and genetic findings in types A and B NPD, and emphasize the seminal contributions of Dr. Brady to this disease. We will also discuss the current status of therapy for this disorder.

Contents

1. Historical overview & contributions of Dr. Brady

The German pediatrician Albert Niemann described the first NPD patient in 1914 in an Ashkenazi Jewish infant who presented with massive hepatosplenomegaly and a rapidly progressive neurodegenerative

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course that led to her death at 18 months of age [1]. We now know this as "type A" NPD. In 1927, Ludwig Pick reviewed the reports of infants with rapidly progressive neurodegenerative disorders and delineated the disease described by Niemann as a unique clinical entity that was distinct from Gaucher disease [2,3]. Although he described this new syndrome as "lipoid cell splenomegaly", in subsequent years it became more commonly known as NPD. Twenty years later the first adult patients with NPD (i.e., "type B") were reported by Pflander and Dusendschon in two Swiss brothers with massive hepatosplenomegaly and no neurologic abnormalities who died at 29 and 33 years of age [4,5].

In 1934, Klenk [6] identified the lipid accumulating in NPD as sphingomyelin, leading to the early suggestion that this disease was due to the lack of an enzyme that catalyzed the degradation of sphingomyelin. In 1966 Brady and co-workers characterized a sphingomyelin-cleaving enzyme from rat liver [7], and shortly thereafter [8] described a deficiency of this enzyme (ASM; EC 3.1.4.12) activity in tissue samples obtained from six infantile NPD patients. Schneider and Kennedy soon confirmed this finding [9] and also reported deficient ASM activity in a 16-year-old male patient who had no neurologic involvement (i.e., "type B" NPD).

Due to the overlapping pathological and clinical features of patients with Gaucher disease and NPD, the differential diagnosis of these disorders remained difficult until in 1967 Brady, Shapiro and colleagues described the first enzymatic discrimination of these diseases by determining the respective enzymatic activities in peripheral blood leukocytes [10]. Similarly, the Brady group delineated another group of patients with overlapping biochemical, pathological and clinical features of types A and B NPD. These patients presented with hepatomegaly, foamy macrophage infiltration into tissues and bone marrow, partial deficiency of ASM activity, and moderate accumulation of sphingomyelin, but also exhibited chronic and often severe neurological deterioration. They were therefore classified as having types C, D or E NPD. In 1980 Brady and Pentchev reported a mouse model with similar clinical and biochemical features to these patients, and went on to show that the ASM deficiency in these mice was secondary to a primary defect in cholesterol esterification [11,12]. In 1985 these same investigators demonstrated a cholesterol esterification defect in cultured cells from type C NPD patients, clearly distinguishing them from types A and B NPD [13]. We now know that type C NPD is due to defects in two distinct cholesterol-binding proteins (NPC1 and NPC2). The nosology of types D and E NPD are no longer used.

Subsequent work led to the isolation of the genes responsible for these disorders (also see the review of type C NPD in this issue), production and characterization of the recombinant proteins, and the development of new therapies. The seminal contributions of Dr. Brady to our early understanding of this disease are summarized in Table 1. Below we will review types A and B NPD and provide information on the state of therapy for this disorder. For the purpose of this review we will use the historical nosology of types A and B NPD, however it should be recognized that since this disorder is due to a continuum of phenotypes arising from mutations in the same (*SMPD1*) gene, it should be more accurately defined as a single disorder, ASM deficiency (ASMD), with acute neurological, chronic neurological, and chronic non-neurological forms.

Table 1
Key publications of Dr. Roscoe Brady on the study of types A and B Niemann-Pick disease.

Citation	Finding
Kanfer et al., J. Biol. Chem., 1966; 24:1081–84.	First purification of acid sphingomyelinase from rat liver.
Brady et al., PNAS, 1966; 55:366–9.	First demonstration that acid sphingomyelinase deficiency was responsible for type A NPD.
Kampine, Brady et al., Science, 1967; 155:86–7.	First enzymatic discrimination of Gaucher and NPD.
Epstein, Brady et al., Am. J. Hum. Genet., 1971; 23:533–35.	First in utero diagnosis of NPD.
Gal, Brady et al., N. Engl. J. Med., 1975; 293:632–6.	First chromogenic assay to detect patients with acid sphingomyelinase deficiency.
Pentchev et al., PNAS, 1985; 82:8247–51.	First demonstration that the metabolic defect in type C NPD was distinct from types A and B NPD.

2. Clinical features & diagnostic evaluation

Type A NPD patients exhibit hepatosplenomegaly and failure to thrive within the first year of life. A cherry-red spot is present in the macula in ~50% of these infants. The disease is characterized by a rapidly progressive neurodegenerative course, with profound hypotonia and failure to attain milestones. Most type A infants do not survive beyond the third year of life [14,15].

In contrast, type B patients have no overt signs of CNS involvement, but hepatosplenomegaly may be profound and accompanied by signs of liver failure [16–18]. Serum triglycerides and LDL-cholesterol are often elevated, while HDL-cholesterol is low. The lungs are frequently involved in type B NPD, and pulmonary function is often compromised. There also may be a reddish-brown halo surrounding the macula in the eyes of these patients, and in some cases a distinct cherry red spot can be identified. Patients with findings intermediate between types A and B NPD also have been described [19].

Because insufficient ASM activity is the hallmark of types A and B NPD, quantifying this enzyme activity in convenient cells such as circulating leukocytes or cultured skin fibroblasts is the standard confirmatory diagnostic procedure [20,21]. Sequencing of the *SMPD1* gene also can be used to confirm the diagnosis, but should not be used as a first line diagnostic indicator. The presence of vacuolated cells in peripheral blood smears or bone marrow is also indicative of the disease, but is not diagnostic in the absence of enzymatic and/or genetic confirmation. Dried blood spot enzymatic assays also have been recently developed to detect types A and B NPD patients [22]. The differential diagnosis of types A and B NPD should include Gaucher disease and type C NPD. Biochemical and/or genetic testing in a reliable laboratory can readily distinguish these conditions.

3. Natural history

Most type A NPD babies are diagnosed in the first 6 months of life during a diagnostic evaluation of hepatosplenomegaly [14,15]. Although hypotonia may be evident within the first few months, development usually progresses somewhat normally until about 6 months of age. From 6 to 15 months development plateaus, followed by a rapidly progressive psychomotor deterioration. Most patients never develop the ability to sit independently. Hypotonia worsens during this period, and the infants become less interactive. Failure to thrive accelerates as the affected infants are unable to consume sufficient calories due to hypotonia, weakened suck, and stomach compression. Most type A babies die before 2 to 3 years of age, often from respiratory failure following pulmonary infection.

The most common initial manifestation of type B NPD is hepatosplenomegaly, which is usually noticed during early childhood, although patients with milder phenotypes have been diagnosed as late as the sixth decade of life. Organomegaly can be significant, with an average splenic volume greater than ten multiples of normal [16–18]. Children with type B NPD often have growth restriction, particularly of linear growth, which is associated with a delayed bone age. Delayed onset of puberty, often by several years, is common [23,24]. Other common disease manifestations include fatigue, bone and joint pain, and osteopenia. Thrombocytopenia and leucopenia typically worsen over time, as does pulmonary function, which shows a restrictive pattern of lung disease with abnormal diffusing capacity of oxygen [25,26]. Patients with a variant form of type B have neurologic features such as ataxia, learning difficulties, and gross motor delays; these

patients generally have more severe systemic manifestations as well [19,27].

Some patients with type B NPD can develop significant life-threatening complications of their disease, including liver failure, hemorrhage, oxygen dependency, pulmonary infections, and splenic rupture [28,29]. Some develop coronary artery or valvular heart disease. The most common causes of disease-related morbidity and mortality are respiratory and liver failure. Almost one fifth of children with type B NPD died during the course of a longitudinal natural history study, suggesting that type B NPD is a serious, life-threatening pediatric disease. Detailed descriptions of the natural history and causes of morbidity and mortality in type B NPD have been published (e.g., [14,16–18,28,29]).

4. Pathology

Large, lipid-laden foam cells are present in the liver, spleen, lymph nodes, adrenal cortex, lung airways, and bone marrow in types A and B NPD [3]. The cells have a mulberry appearance because of an accumulation of lipid droplets that stain for phospholipids. Some cells are pigmented because of the presence of ceroid. Electron microscopy often reveals concentrically lamellated, myelin-like figures. The brain of type A NPD patients is usually atrophic. Ganglion cells are often swollen, and the cytoplasm is pale and vacuolated. Within these cells are membrane-bound inclusions. There is a loss of cells in the cerebral and cerebellar cortices of type A infants, along with gliosis in both gray and white matter. Some areas of the white matter show demyelination. Foam cells are present in the leptomeninges, tela choroidea, endothelium, and perivascular spaces of cerebral blood vessels. The basal ganglia, brainstem, spinal cord, and autonomic ganglia also may show morphologic alterations. Little is known about structural changes in the brains of patients with type B NPD.

Foam cells also are present in the hepatocytes, Kupffer cells, and bile duct epithelium in the livers of types A and B patients. Liver biopsies from a cohort of 17 type B NPD adults revealed that most of the specimens showed some degree of fibrosis ranging from minimal to frank cirrhosis [30]. Studies in the mouse model of NPD (ASMKO mice; see below) have shown that ASM deficiency leads to overexpression of cathepsin B and promotes liver fibrosis, consistent with these clinical findings [31]. Sphingomyelin storage also has been demonstrated in multiple types of other cells, including dermal fibroblasts, macrophages, vascular endothelial cells, vascular smooth muscle cells, perineurium, and Schwann cells [30]. Lipid filled macrophages and neutrophils also are found in the airways of types A and B NPD patients, and studies in the ASMKO mice have shown that these airway macrophages are functionally defective [32].

5. Disease mechanism

The principal accumulating lipid in patients with types A and B NPD is sphingomyelin (ceramide-phosphocholine), a major component of cell membranes and a principal phospholipid of the myelin sheath [33,34]. In addition to sphingomyelin, elevated levels of bis(monoacylglycero)phosphate (BMP) and lysosphingomyelin (sphingosine phosphocholine) are common as well [35,36]. Cholesterol (see below), glucocerebroside, lactosylceramide, and gangliosides, particularly ganglioside GM_3, also are elevated, but not so much as in type C NPD.

The enzyme defective in types A and B NPD, acid sphingomyelinase (E.C. #3.1.4.12), has its highest activity at reduced pH and catalyzes the hydrolytic cleavage of sphingomyelin in lysosomes, producing phosphocholine and ceramide (*N*-fatty acylsphingosine) [37,38]. Within lysosomes ASM interacts with other lipid hydrolases and performs an essential housekeeping function by maintaining proper sphingolipid homeostasis and participating in membrane turnover. Notably, when cells are subjected to stress, ASM rapidly translocates from lysosomes to the outer leaflet of the plasma membrane, where it also can hydrolyze sphingomyelin into ceramide [39,40]. This causes reorganization of membrane lipid microdomains, or "raft" structures, and stimulates downstream signaling events.

These observations suggest that the clinical findings in types A and B NPD may be due, at least in part, to lipid abnormalities in the plasma membrane as well as lysosomes, resulting in downstream abnormalities in cell signaling pathways. This has been particularly well documented in the brains of ASMKO mice (see below), where sphingomyelin storage in the neuronal membranes leads to abnormal synapse formation and function and other abnormalities [41–43]. It is unclear whether the activity of ASM at the plasma membrane occurs in acidified "micro" compartments, or proceeds at a non-acidic pH. Of interest, despite the acidic pH optimum of the enzyme and essential housekeeping function in lysosomes, Tabas and co-workers have demonstrated that ASM can hydrolyze sphingomyelin present in blood lipoproteins at physiological pH [44].

One product of sphingomyelin hydrolysis by ASM is the lipid ceramide, an important signaling molecule that is elevated in many common diseases (e.g., diabetes, fibrosis, sepsis) [45–47]. ASM is a major source of ceramide, both in lysosomes and at the cell membrane. While it may be hypothesized that defective ASM activity in types A and B NPD results in depleted ceramide, surprisingly, ASMKO mice have elevated ceramide in their tissues. This is likely due to breakdown of the accumulated sphingomyelin by other sphingomyelinases present in non-lysosomal compartments. Moreover, abnormalities in downstream products of ceramide hydrolysis, sphingosine and sphingosine-1-phosphate, also are elevated in ASMKO mouse tissues. These potent signaling lipids may be contributing to NPD disease pathogenesis as well.

The primary organ systems affected in all ASM-deficient patients are the spleen, liver and lung. As noted above, lipid filled foam cells can be readily detected in these tissues, as well as in the pulmonary airways. The onset and severity of pulmonary disease in ASM-deficient NPD is highly variable, and is primarily due to the infiltration of inflammatory cells into the airways [25,26]. In ASMKO mice (see below), the infiltration of these cells can be correlated with the elevated release of lung chemokines, including MIP1alpha [32]. Once present, inflammatory airway cells can be very long-lived, and in the case of ASMKO mice also exhibit defective phagocytosis and other biological properties.

Foam cells (often referred to as "NPD" cells) are readily detected in the bone marrow of type A and B NPD patients. It is notable that many patients exhibit joint and bone pain, and there may be a higher incidence of fractures as well [24]. There is a growing literature showing the importance of sphingolipids, and sphingomyelin/ceramide in particular, on normal cartilage and bone homeostasis [48], and it is possible that the accumulation of these lipids within bone, bone marrow and cartilage may be contributing to these features of the disease.

Due to the cellular abnormalities in the liver and spleen, ASM-deficient NPD patients often present with abnormal hematological and plasma lipid findings. For example, low platelets are a common finding in the disease, as is the combination of very low HDL cholesterol, high LDL cholesterol, and high triglycerides [49]. The consequences of these lipid abnormalities on cardiac disease in type A and B NPD is not clearly understood, although as mentioned above there is evidence for early cardiac calcifications and cardiovascular disease in some patients. Growth abnormalities also are frequently found in children with ASM deficiency, and may be due to abnormalities in the IGF-1 signaling pathway [23].

Although little is known about brain pathology in ASM-deficient NPD patients (see above), recent studies in the ASMKO mice have revealed numerous abnormalities, including Purkinje cell death in the cerebellum, as well as abnormal synaptic vesicle release and uptake and defective calcium homeostasis, neuronal polarization, myelin production and immune responses (for review see [50]).

6. Molecular genetics

ASM is produced from a single gene (*SMPD1*) located within the chromosomal region 11p15.4 [51,52]. This region of chromosome 11 is

a hotspot for imprinting within the human genome, and studies have shown that the *SMPD1* gene is preferentially expressed from the maternal chromosome (i.e., paternally imprinted) [53]. Types A and B NPD are inherited as recessive traits, and the degree of clinical involvement largely depends on the type of *SMPD1* mutations inherited. However, because the *SMPD1* gene is imprinted, the phenotypes also may be due, at least in part, to inheritance of specific mutations on the maternal versus paternal alleles. It is of interest that abnormal clinical and laboratory findings have been reported in heterozygous individuals carrying only one *SMPD1* mutation [54]. This could similarly be due to inheritance of a single, "severe" *SMPD1* mutation on the preferentially expressed maternal chromosome.

To date, >180 mutations have been found within the *SMPD1* gene causing types A and B NPD (e.g., [55,56]). These include point mutations (missense and nonsense), small deletions, and splicing abnormalities. No hotspots exist for these mutations. Several polymorphisms also have been found within the *SMPD1* gene of normal individuals, including a varying number of repeated nucleotides within the region encoding the ASM signal peptide [57]. The effects of this polymorphism on ASM trafficking and function have not been systematically studied. Also of note, similar to another sphingolipid storage disorder (Gaucher disease), genetic variants within *SMPD1*, including some mutations causing types A and B NPD, have recently been identified as risk factors for Parkinson disease [58,59].

Identification of mutations in type A and B NPD patients has permitted the first genotype–phenotype correlations for this disorder, and the first genetic screening efforts [60]. For example, three mutations account for ~90% of Ashkenazi Jewish type A NPD infants. This observation led to DNA-based carrier screening of Ashkenazi adults, and revealed that the carrier frequency for these three mutations in the Ashkenazi population is between 1:80 and 1:100 [60]. Another mutation, deltaR608, only occurs in type B NPD patients and is found in 15% to 20% of NPD type B individuals in Western Europe and North America [55]. Another mutation, Q292K, is associated with the intermediate neurological phenotype [19]. These and other findings have assisted physicians, genetic counselors and families in predicting the phenotypic outcome in individual NPD patients, and in the future may lead to large-scale screening for this disorder in specific populations. For example, one particularly interesting recent study examined a single mutation (A359D) that occurs in >90% of type B patients in Chile [61]. Screening for this mutation among healthy individuals living in Santiago indicated that the carrier frequency for type B NPD within Chile was ~1/106, predicting a disease incidence of ~1/45,000. To facilitate further genotype-phenotype and mutational analysis, the crystal structure of recombinant ASM also has recently been reported [62,63].

7. Animal models

Two ASM knockout (ASMKO) mouse models have been produced [64,65]. Homozygous animals exhibit progressive lipid storage in reticuloendothelial organs, as well as in the brain. The principal accumulating lipid is sphingomyelin, but cholesterol and ganglioside storage also has been observed. Progressive loss of Purkinje cells in the cerebellum leads to gait abnormalities, and affected animals die within 6 to 8 months. The precise cause of death is unknown, but is likely secondary to the neurological phenotype.

Profound inflammatory disease also has been documented in the ASMKO mice, and is a major contributing feature of the pulmonary and neurological phenotypes [32]. Pulmonary lavage has revealed numerous inflammatory cells in the air spaces of ASMKO animals, and the release of many inflammatory cytokines into the lavage fluid. These observations and microarray analysis of ASMKO lung and brain tissue identified several inflammatory molecules that may be used as biomarkers to monitor disease progression and treatment response [66]. Inflammatory biomarkers, including chitotriosidase and CCL18, are elevated in NPD patients as well [67].

In addition to the above-noted phenotypes, the ASMKO mice also exhibit a defect in ceramide-mediated signal transduction. This has been studied mostly in the context of stress-induced apoptosis, where the ASM deficient mice are resistant to cell death induced by several treatments (e.g., irradiation, ischemia) [37]. Although many cell types exhibit this resistant phenotype, it is most evident in endothelial cells. Presumably, the lack of functional ASM inhibits the production of ceramide and reorganization of membrane rafts following stress, protecting against cell death. ASMKO cells also are resistant to infection by various pathogens, likely also due to defects in membrane reorganization and internalization of the pathogens via receptors [68]. It is also of interest that oocytes from ASMKO mice do not undergo normal apoptosis as they age [69]. This is similarly due to the lack of ASM and failure to produce ceramide in response to normal developmental signals.

In addition to the ASMKO models, a transgenic mouse model of type B NPD has been produced [70]. This animal was engineered by introducing a partially functional mouse *SPMD1* gene onto the complete ASMKO background. The end result was a mouse that produced from 8% to 15% residual ASM activity in most organs. These mice never developed a neurological phenotype and had normal longevity. However, by about 8 to 10 months of age they began to exhibit lipid storage in reticuloendothelial organs. These observations provided the first direct, in vivo evidence that low levels of ASM activity in the brain are likely to prevent or substantially slow neurological disease in NPD patients.

Lastly, knock-in models of types A and B NPD have been constructed [71]. In these models the common type NPD A mutation – R496L, and the common type B mutation – deltaR608 were introduced. The phenotypes of these mice were as expected. R496L mice developed a severe "type A" phenotype indistinguishable from the knockout mice. DeltaR608 developed a later onset, non-neurological "type B" phenotype. They expressed between ~5 and 10% residual ASM activity in the brain, again demonstrating that low level ASM activity was neuroprotective.

Canine and feline models of type A NPD have been described, but no colonies are currently available.

8. Therapy for types A & B NPD

8.1. Historical

Bone marrow transplantation (BMT) has been undertaken in several ASM-deficient NPD patients. Reduction in liver and spleen size has been documented following BMT, although complications secondary to the transplant procedure may be severe [72]. The effect of BMT on the neurological phenotype of type A NPD patients also has not been adequately shown, although this procedure has been extensively studied in the ASMKO mouse model [73]. Overall, when BMT was undertaken in these mice during the newborn period and engraftment levels were high (90%), the positive effects on the reticuloendothelial organs were profound. However, even under such "optimal" transplant conditions, the effects on the CNS were intermediate and animals died secondary to a neurological phenotype. This could be improved by direct intracranial injection of bone marrow-derived cells to provide a local source of ASM in the CNS, but even under these conditions the progressive neurological disease was not prevented [74]. Thus, based on these animal studies it may be predicted that even in the "best case" scenario BMT is likely to have a very modest effect on slowing the CNS disease in type A NPD infants. In addition to BMT, liver and amniotic cell transplantations also have been undertaken in ASM deficient NPD patients, although the outcomes of these procedures have not been fully described [75–78]. In one recent report [79], two adult type B NPD patients underwent liver transplants with some positive effects on liver function.

8.2. Enzyme Replacement Therapy (ERT)

The gold standard of achieving widespread enzyme delivery to organs of pathology in LSD patients is ERT. Based on the pioneering

development of such therapy for Gaucher disease by Brady and colleagues in the 1980s [80], ERTs are currently available for 7 LSDs and under development for several others, including ASM deficiency. To evaluate ERT for this disorder, recombinant human ASM (rhASM) has been produced in Chinese hamster ovary cells and extensively characterized [81]. The recombinant enzyme was then administered by tail vein injection to young ASMKO mice, and the lipid storage and associated pathology could be effectively prevented in the reticuloendothelial organs [82]. In addition, the progressive inflammatory disease was prevented in these organs. The effects of the enzyme were dose dependent and were most profound in the liver and spleen, followed by the lung. As predicted from the experience in other LSDs, there was no effect on the progression of neurological disease, and the treated ASMKO animals died at the same age as untreated mice. rhASM also was used to treat ASMKO mice with established disease, and significant reversal of lipid storage and histological improvement of reticuloendothelial organs was demonstrated.

These studies in the ASMKO mice also revealed a dose-dependent toxicity that was not observed in animal models of other LSDs [83]. This has been attributed to the rapid release of ceramide from sphingomyelin when rhASM was administered at high doses, and could be prevented by dose escalation to "de-bulk" the stored sphingomyelin and maintain a low level of ceramide release. After such "dose escalation", high levels of rhASM could be administered to the ASMKO mice without toxic effects.

These and other findings in the ASMKO mice have led to clinical trials evaluating ERT in non-neurologic ASMD patients (sponsored by Genzyme/Sanofi). A phase 1 safety study was first undertaken in adult patients. Eleven patients were treated with single administrations of rhASM (olipudase alfa®) of increasing doses once every 2 weeks [84]. No serious adverse events were observed, and safety findings included only transient elevation of serum cytokines and bilirubin. Based on these results, the maximum starting dose of rhASM was determined to be 0.6 mg/kg. Next, a phase 1b repeat dosing study was undertaken in 5 adult patients who were treated for 26 weeks [85]. As in the mouse model, a dose escalation scheme was used where patients first received several low doses to de-bulk the sphingomyelin in tissues, followed by escalation to a maximum dose of 3 mg/kg. All patients were successfully dose escalated without serious adverse events. Reductions in sphingomyelin storage, spleen and liver volumes, and serum chitotriosidase activity, as well as improvements in infiltrative lung disease, lipid profiles, platelet counts and quality of life assessments were observed. Each of the 5 patients have been continued on treatment during an extension period, and evaluation at up to 18 months of treatment revealed that mean spleen volumes reduced from 12.8 multiples of normal (MN) to 7.7; mean liver volumes form 1.7 MN to 1.1; and mean percent predicted DLco increased from 58.8% to 76.4%. Triglycerides were reduced by 42.6%, cholesterol by 12.4%, LDL cholesterol by 15.4%, and HDL cholesterol increased by 78.9% [86]. The drug was well tolerated with no deaths, serious adverse events, or adverse events that led to discontinuation of the study. None of the 5 patients developed anti-drug antibodies.

Based on these findings, the FDA granted "Breakthrough Designation" to this therapy in 2015 and two additional clinical trials are currently underway [87]. One is a phase 2 study in pediatric ASMD patients (NCT02292654) that follows a similar dose escalation protocol to the phase 1b adult study described above, and the second is a double blinded phase 2/3 study in adult patients (NCT02004691). Patients have been dosed in both studies and the evaluations are ongoing.

8.3. Other therapies

Based on the above, it is predicted that ERT will be safe and effective for the non-neurologic features of ASM deficiency. However, such therapy still requires biweekly infusions of recombinant enzyme and is not likely to be effective for the CNS components of the disease. Thus, it is important to continue to evaluate new therapeutic approaches. Among these, gene therapy has been extensively studied in the ASMKO mice, including autologous hematopoietic stem cell gene therapy using retroviral vectors [88], liver directed gene therapy using AAV vectors [89], and direct injection of gene therapy vectors with or without rhASM into the brain [90,91]. Overall, expression of ASM in the mouse using gene therapy vectors has proven safe and effective. However, to achieve significant pathological improvements in the brain, direct injection of the vectors is required. It is also important to note that while this approach has proven effective in the mouse model, dissemination of such vectors and widespread expression of ASM in larger brains has not been demonstrated, nor have the long-term effects of this treatment. In addition, given the known acute toxicity associated with elevated ceramide release, dosing of the gene therapy vectors must be carefully monitored since there is no effective way to turn off expression once they are introduced.

Recently, neurological improvements also were obtained in the ASMKO mice using a novel pharmacological therapy to enhance the activity of neutral sphingomyelinase [92]. This approach is based on the concept that some pathology in ASM deficient NPD is due to sphingomyelin accumulation outside of lysosomes that may be accessed by other sphingomyelinases. Another approach likely to be studied in the future will be anti-inflammatory therapies. As noted above, in types A and B NPD, as in other LSDs, inflammation is a widespread and important secondary aspect of the disease, and therapies that target inflammation are likely to be important adjuncts to those that directly restore the missing enzymatic activities (e.g., ERT, gene therapy). Chaperone therapies also are likely to play a role in the treatment of this disease, as in other LSDs. In this regard Kirkegaard et al. [35] have shown that Hsp70 stabilizes lysosomes by binding to the lysosomal membrane lipid, bis(monoacylglycero)phosphate and activating ASM [35]. Notably, the reduced ASM activity in types A and B NPD cells could be restored by treatment with Hsp70. Molecular chaperones that bind directly to ASM also may be of use to restore the defective enzymatic activity and/or to stabilize the infused recombinant enzymes, as is being used in other LSDs [93].

9. Conclusions & future directions

Since the discovery of the first patients with NPD over a century ago, tremendous progress has been made in deciphering the pathophysiology of this disease and in the development of new treatments. Based on the seminal contributions of Dr. Brady and his colleagues, we now know that there are two distinct metabolic abnormalities that account for these patients – ASM deficiency in types A and B NPD and cholesterol esterification in type C NPD. In the latter group we also know that there are two distinct gene and protein abnormalities that may be responsible for the abnormal cholesterol metabolism (NPC1 and NPC2). Further, the Brady laboratory developed methods to diagnose these diseases in vitro, and to clearly distinguish them from Gaucher disease and other lipid storage disorders. Moreover, his seminal work on the development of ERT for Gaucher disease and the identification of ASM deficiency as the underlying cause of types A and B NPD, opened the door for the development of ERT for this disorder as well.

Although ERT is likely to become available for patients with ASM deficiency in the near future, it is also unlikely to impact the neurological features of the disease. Future research should therefore be focused on achieving widespread enzyme delivery to the brain, as well as developing alternatives to enzyme infusions, including gene therapy and small molecule approaches. The recent crystal structure of recombinant ASM and the development of new and safe gene therapy vectors should facilitate these approaches. In addition, adjunct therapies, including anti-inflammatory and other approaches, should be evaluated. Further investigation of the organ-specific pathology in types A and B NPD also is essential to continue to identify these new and alternative disease targets. Finally, given the impact of end stage fibrosis and tissue damage,

particularly in the liver and brain, early diagnosis and treatment of the disease is required, and will be facilitated by the implementation of newborn and other screening activities. In this regard improved genotype/phenotype correlations are required to help families better understand the impact of the diagnosis on the health and well being of their child.

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Conflict of interest

E.H.S. and R.J.D. are inventors on patents that have been licensed by Mount Sinai to Genzyme regarding the treatment of types A and B NPD, and may generate royalty income for themselves and Mount Sinai. E.H.S. also receives research funding for types A and B NPD from Genzyme, and is a consultant on types A and B NPD to Genzyme.

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