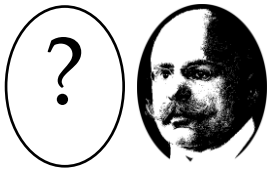
Pfrieger's Digest



Issue 15
September – December 2025

Niemann-Pick Diseases

Summaries of latest research advances related to Niemann-Pick diseases, acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD), based on selected peer-reviewed publications in scientific journals.

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Dear Readers.
Welcome to the **fifteenth** issue covering September 1st 2025 to December 31st 2025. The corresponding links for the PubMed queries are:
- for **NPCD**:

((niemann-pick c OR niemann-pick type C OR niemann-pick type C1 OR niemann-pick type c2 OR npc1 OR npc2) AND (("2025/09/01"[Date - Publication] : "2025/12/31"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2025/08/31"[Date - Publication]))

- for **ASMD**:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2025/09/01"[Date - Publication] : "2025/12/31"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2025/08/31"[Date - Publication]))

During this period, **59** (NPCD) and **41** (ASMD) articles were published in scientific journals including **9** (NPCD) and **5** (ASMD) reviews. **Two** articles appear in both queries. Note that English versions of the Digest are accessible through the open science archive HAL!

Please note: 1) My selection of articles is subjective. 2) I comment only peer-reviewed original articles, and neither preprints nor review articles nor case studies describing single patients. 3) I only include articles that I can read from start to end. 4) I try to ensure correctness of statements, but I cannot guarantee this. 5) Errors of any kind are not excluded. 6) My judgements and interpretations are subjective and reflect my personal opinion, they do not claim any validity. 7) I apologize for any errors in grammar, punctuation and orthography, and for any wrong, quirky or otherwise weird expressions. 8) This text is my translation of my original German version, which was written by myself thanks to my own natural and naturally limited intelligence without any help from an artificial one. 9) Feel free to distribute this issue, as long as there are no changes to the text or layout. 10) Translations to other

languages are welcome, as long as my authorship and the original version are mentioned. 11) The digest does not indicate sources of funding for published studies. This information can be found in a dedicated section of each publication. 12) English versions are freely available from the open science archive HAL, issues 2-6 will be uploaded. 13) I thank the German Niemann-Pick Selbsthilfegruppe e.V. and NPSuisse for support and all others who kindly host the Digest on their websites or distribute it otherwise.
14) Feedback (praise, criticism, giftcards) welcome to: fw-pfrieger@gmx.de.

Patients (NPCD)

PMID:41260183 Porter FD, Alexander DM, Albert OK, Robbins KP, Labor DA, Borruso AJ, Farhat NY, Jiang X, Berry-Kravis E. Utility of 24(S)-hydroxycholesterol as a proximal biomarker to monitor long-term intrathecal adrabetadex therapy in individuals with Niemann-Pick disease, type C1. Mol Genet Metab. 2025 Dec;146(4):109254. doi: 10.1016/j.ymgme.2025.109254.

Let's start easy, with a short but important contribution to the unavoidable biomarker topic, here 24-Hydroxycholesterol. This stuff is produced by nerve cells and indicates their cholesterol metabolism. The study with 10 NPC patients with disease onset between 0 to 13 years shows a measurable increase in 24OH concentration 48 hours after intrathecal administration of hydroxypropyl-beta-cyclodextrin in seven out of 10 patients. Further evidence that the treatment works and that the hydroxy-stuff is a valid marker.

PMID:41529425 Agrawal N, Bianconi S, Jaeger R, Farhat NY, Alexander DM, Sinaii N, Hadigan C, Berry-Kravis E, Porter FD. Characterization of liver disease in a cohort of individuals with Niemann-Pick Disease, Type C1. Mol Genet Metab. 2025 Dec 29;147(3):109716. doi: 10.1016/j.ymgme.2025.109716.

Another study from the Berry-Kravis / Porter vaults, now the liver. "Liver, wait a minute?" you may think "Ok, it's affected in NPCD, nothing new, we know!". Well, think again, in fact, not much is known about the liver damage and possible relations to other symptoms. Based on data (ultrasound, stiffness, enzymes) from 93 NPCD patients the authors distinguish three groups concerning liver disease at birth: *nada* (32% of cases), mild/moderate (jaundice, hepatosplenomegaly; 43%), and severe (cholestasis, ascites, hepatitis; 22%). One important finding: patients with any liver damage at birth present neurologic symptoms on average four to six years early than those without. Well, what does "on average" a.k.a. mean values mean in a disease with variability (standard deviations) as broad as the Eiffel tower high. A key question is what causes

these differences in liver damage, is it the NPC1 mutation, or other genes, or something else, or all of this together. Hopefully, this precious dataset can be explored further.

PMID:41274250 Diksha, Gaurav V, Kamla D, Mathuria YP, Kapshikar R, Kumar A, Gupta SK, Ghosh DK. Non-invasive and rapid diagnosis of Niemann-Pick disease type C1 by immunocytochemical detection of leaky lysosomes in squamous epithelial cells. Biochem Biophys Res Commun. 2025 Dec 31;793:152969. doi: 10.1016/j.bbrc.2025.152969.

Colleagues from India propose a new, relatively fast and cheap diagnosis test. It is based on a protein named galectin-3 and a mouth swab. Galectin-3 enters damaged lysosomes, where it can be detected by a staining method (for illuminati: immunocytochemistry), and it has been proposed as blood biomarker. The oral swab contains buccal squamous cells, whose lysosomes are damaged in NPCD. The results suggest that the test works. A first step, more have to follow: how reliable, how specific, how sensitive.

Patients (ASMD)

PMID:40937531 Scarpa et al. (2025) Long-Term Safety and Clinical Outcomes With Olipudase Alfa Enzyme Replacement Therapy in Children and Adolescents With Acid Sphingomyelinase Deficiency. J Inherit Metab Dis. 2025 Sep;48(5):e70086. doi: 10.1002/jimd.70086.

The article provides a first answer to the question how young patients with chronic visceral form (a.k.a. type B) are after long-term treatment with olipudase. The data were collected in the Sanofi sponsored ASCEND-PED study. Spleens and livers reached in nearly all patients normal size ranges after four to six years of treatment. Height, lung function, and plasma measures of cholesterol, LDL und HDL, lysosphingomyelin and chitotriosidase, which indicates active macrophages, improved. No new adverse effects occurred compared to what has been reported (Digest 8; Dias et al., 2021, 2022).

PMID:41029409 Morsy et al. Real-life impacts of olipudase alfa: experiences of adults receiving enzyme replacement therapy for acid sphingomyelinase deficiency-results from an international survey study. Orphanet J Rare Dis. 2025 Sep 30;20(1):493. doi: 10.1186/s13023-025-03997-6.

This publication from the "INPDA laboratories" is about real life, real life of ASMD patients before and during treatment with olipudase. Similar to a previous study with young patients published in 2024 (Raebel et al., Digest 10) here adult English-speaking patients filled out an online survey, some were interviewed afterwards. The data are from 11 patients. This may seem little, but hey, it's a rare disease, and there were inclusion criteria including treatment with olipudase that – unfortunately – is not available to all patients. Half of the patients presented first symptoms before the age of two years. The results are clear, the burden imposed by symptoms is huge, and it is reduced by the treatment. Just as an example: all patients showed abdominal pain and shortness of breath before treatment, most of them weekly or more often. During the treatment, these symptoms were gone in nearly half of the patients (40%), the rest presented monthly or weekly. It's not clear how long patients were treated though. Hours-long infusions are tolerable, but pills would be better, even a one-shot gene therapy.

Patients (ASMD and NPCD)

PMID:41429203 Sidorina A, Catesini G, Deodato F, Boenzi S, Martinelli D, Rizzo C, Dionisi-Vici C. New multiplex LC-MS/MS method for lipid biomarker analysis of inherited neurodegenerative metabolic diseases. J Lipid Res. 2025 Dec 20;67(1):100967. doi: 10.1016/j.jlr.2025.100967.

Back to biomarkers, watchword: "Seven at one blow". The study is about another new multiplex assay, i.e. simultaneous measurements of several biomarkers in blood. This is nothing new (s. Ducatez et al. 2025; Digest 12), new is which biomarkers, and which and how many samples. This is notably important for newborn screens aiming to detect as many diseases as possible. The study shows that simultaneous measures of lysosphingomyelin and N-palmitoyl-o-phosphocholineserine (a.k.a. lysosphingomyelin-509) in plasma can distinguish between ASMD (7 patients) and NPC (16 patients). With respect to newborns, there were similar differences albeit with smaller sample sizes (ASMD: n = 2; NPC: n = 7). The question is whether the approach works also with other patient cohorts.

Animal models (NPCD)

PMID:41456743 Tait S, Fratini F, Boussadia Z, Gaddini L, Marra M, Le Pera L, Venturini G, Ferrante A. Investigation of dipyridamole-elicited signaling in the brain of Niemann Pick type C mice: A multi-omic study. Brain Res Bull. 2026 Jan;234:111708. doi: 10.1016/j.brainresbull.2025.111708.

All good things come in three, here it's a third publication (Digest 6, 12). This is about the drug dipyridamol, an "old" treatment for thrombosis and embolism. It inhibits the uptake of adenosine into cells and specific enzymes (for connaisseurs: phosphodiesterases). Adenosine is an important run-of-the-mill molecule that regulates alone or linked to other molecule countless cellular processes. The previous studies showed positive effects of dipyridamol in patient fibroblasts and in NPC1-deficient mice. The new work is a veritable comparison orgy of transcriptome (gene expression) and proteome data (protein production) from mice and provides possible explanations for the groups' previous findings. It shows that two brain regions, the hippocampus (its shape is sea horse-like) and the cerebellum react differently to NPC1 deficiency and dipyridamol. The differences suggest that neurons in the cerebellum degenerate faster than in the hippocampus because of different activation states of microglial cells. Dipyramidol seems to affect only the hippocampus, where it activates a specific signaling pathway (for afficionados: cGMP-PKG). Maybe a new therapeutic drug target?

Animal models (ASMD)

PMID:41024105 Xiong et al. Modular inflammation network discovery from large-scale phenotypic screening in genetically heterogeneous mouse brains. J Neuroinflammation. 2025 Sep 29;22(1):218. doi: 10.1186/s12974-025-03556-7.

Here's an example of "always expect the unexpected" and of companies doing useful things – ok, just a joke. The study from Genentech, THE biotech-bedrock-*powerhouse*, aimed to understand inflammatiory reactions in the brain, the signals, the players, their networks. To get at this, they undertook a Herculian effort and analysed a huge number of genetically modified mice. And BINGO, one of them has a mutation in the *Smpd1* gene encoding ASM, the protein variant is C248S. Here, "only" inflammation-relevant changes in the brain were studied. It would be great to know how the mice are doing (symptoms, life-span, etc.).

PMID:40888736 Rovic et al. Acid sphingomyelinase is a gatekeeper of placental labyrinthine architecture and function. Development. 2025 Oct 1;152(19):dev204425. doi: 10.1242/dev.204425.

And on with surprises. The study shows that the enzyme ASM is required for normal formation of the placenta, at least in the mouse. In mice lacking ASM, the placenta showed changes that impede the development of the fetus, notably in the socalled labyrinth. This is where maternal and fetal blood vessels meet and where exchange of metabolites happens. Note that the placenta is made to a large extent by cells from the fetus and only part of this part-time organ comes from the mother. Therefore, not surprisingly, transplantation of ASM-deficient embryos to the uterus of healthy mouse mothers did not compensate their growth restriction.

PMID:41106691 Beard CA, Hermanson KN, Snider JM, Hara A, Dahl BK, Allopenna JJ, Marron MT, Newcomb B, Low BE, Wiles MV, Jenkins RW, Obeid LM, Hannun YA, Snider AJ. Retention of lysosomal acid sphingomyelinase protects from Niemann-Pick Disease. Neurobiol Dis. 2025 Nov;216:107147. doi: 10.1016/j.nbd.2025.107147.

And another animal model for ASMD, snipped with the gene scissor CRISPR-CAS to produce a specific variant of ASM called S505A. This variant corresponds to human S507A, same amino acid change two pearls further down the chain. Why? It is well known that one form of ASM does not work in the lysosome. Instead, it is released from cells, notably as part of inflammatory processes. There are many ideas what the enzyme does outside the cells. The question here was: how's the mouse, if it expresses the S505A variant that cannot be released. *Tutto posto*! The mouse is fine, no visceral or neurologic symptoms. It remains to be seen, how this mouse reacts to inflammatory processes.

PMID:41214365 Tzou FY, Hong CL, Chen KH, Vaughen JP, Lin WS, Hsu CH, Rivas-Serna IM, Hsu KY, Ho SM, Panganiban MR, Hsieh HT, Li YJ, Hsiao Y, Yeh HC, Yu CY, Tang HW, Chou YH, Wu CL, Lo CC, Mazurak VC, Clandinin MT, Huang SY, Chan CC. Functional profiling and visualization of the sphingolipid metabolic network in vivo. EMBO Rep. 2025 Dec;26(24):6380-6417. doi: 10.1038/s44319-025-00632-0.

For change, here's a publication that's like "dream sweet dreams!". Again, it's about animal models, now the fruitfly, for the initiated *Drosophila melanogaster*, the supermodel for genetic manipulation orgies. Here, models for all (!) 52 components involved in sphingolipid metabolism were generated, including the fly version of ASM. Another herculean effort! The colleagues show that in the fly brain, ASM is made mainly by glial cells and not by neurons. Seemingly, there is task sharing between nerve and glial cells with respect to sphingolipid metabolism (see below Sandhoff). Why dream? Imagine, one could generate all these models in mice.

Cell-based Models NPCD

PMID: 40963079 Moiz B, Vargas VA, Brandon KD, Sangha G, Weber C, Li A, Pepper T, Walls M, Qin A, Hart S, Davidson C, Stroka K, Porter FD, Clyne AM. Cholesterol Depletion with U18666A and Methyl-β Cyclodextrin Increased Small Molecule Permeability Across Brain Microvascular Endothelial Cells. Ann Biomed Eng. 2025 Nov;53(11):3222-3236. doi: 10.1007/s10439-025-03841-9.

Barrier-free access is great, but not for the brain. It would be terrible, if all the stuff that floats in the blood would get in. On the other hand, it would be great, if therapeutics be it drugs, viruses, or cyclodextrin could enter. This is prevented by a physical barrier between the brain and blood vessels, O-ring like structures called *tight junctions* that are formed by socalled endothelial cells (s. Digest #7). Some fatty substances overcome the barrier passing through cell membranes like the "Le passe muraille". We know surprisingly little about the blood brain barrier in NPCD. Is it broken? There are no studies in patients, and very few in mice. The new work addresses the question using a cell culture model that imitates some but not all properties of the barrier (s. Digest 12). The work shows that treatment of cells with U18666A, which inhibits NPC1, or with high doses of methyl-beta-cyclodextrin perforates the barrier. The effect of the Ulalala

drug is repaired by lower concentrations of hydroxypropyl-beta-cyclodextrin. The unavoidable question is what these results have to do with the situation in patients.

PMID: 41452985 Ndoj K, Tantucci M, Sanza P, Zubak K, Marodin G, Kingma J, Snijder F, Veenendaal T, Kober DL, Zelcer N, Klumperman J. NPC1 trafficking via VPS41-dependent LAMP carriers regulates endosomal cholesterol homeostasis. Proc Natl Acad Sci U S A. 2025 Dec 30;122(52):e2521979122. doi: 10.1073/pnas.2521979122.

Here some fundamental stuff. The question is simple: how does the excavator get to the construction site or the NPC1 to the lysosome. Depending on the protein, manufacturing requires several steps in different locations. In one place, the amino acid chain is made (endoplasmatic reticulum) and elsewhere, the protein clump is refined (Golgi apparatus). From there, it has to reach its workplace. Several studies have addressed this topic using a not so genuine technical approach: cells were forced to make a labeled version of NPC1 brought in from outside. The Zelcer lab succeeded in labeling the cell's own NPC1 version thereby allowing to track its natural path in the notorious HeLa cell line (see Digest 10). The results reveal a new pathway, small transport vesicles that carry presorted NPC1 and LAMP1 from the Golgi apparatus to the lysosome. The pathway requires a protein with the wonderful name VPS41. Whether this pathway works in "real" cells remains to be seen.

Molecule (NPCD)

PMID: 41026540 Pan X, O'Hare J, Mowdawalla C, Mota S, Wang N, Hussain MM. Bmal1 is involved in the regulation of macrophage cholesterol homeostasis. JCI Insight. 2025 Sep 30;10(21):e194304. doi: 10.1172/jci.insight.194304.

PMID:40097742 Deota S, Pendergast JS, Kolthur-Seetharam U, et al. The time is now: accounting for time-of-day effects to improve reproducibility and translation of metabolism research. Nat Metab. 2025;7(3):454-468.

Once more, bycatch! Pan et al. is not about NPCD, but the results may be important for the community. The authors report that the cellular production of NPC1 and NPC2 are regulated by a *clock gene*. These *clock genes*, including *Bmal1*, are switches that regulate together with the ambient light how the body adapts to the day/night cycle. The results show: if Bmal1 is missing, the production of NPC1 and NPC2 goes down, at least in

macrophages. The results provoke the question whether cellular production of NPC1 and NPC2 changes during the day/night cycle in the liver, the brain, or other corners of the body.
In this context, and exceptionally, the review by Deota et al. may be mentioned, a must read for anybody studying NPCD or ASMD or any other disease preclinically or clinically. This is about metabolic changes during the day/night cycle and their influence on anything related to diseases, symptoms, biomarkers, and drug effects.

PMID: 41271739 Lv H, Yang H, Guo X, Li J, Xie Y, Jiang C, Shi J, Huang Q, Shao D. Mechanism of LEPR-mediated cholesterol metabolism involved in NK cell function suppression under simulated microgravity. NPJ Microgravity. 2025 Nov 21;11(1):83. doi: 10.1038/s41526-025-00473-0.

Similar topic, important information for astronauts, and all those who'd like to be: Microgravity lowers the production of NPC1 and NPC2 in natural killer cells, main actors of the immune system. No reason for envy, the cells were not in space, only in a kind of advanced salad spinner or more precisely a rotating wall vessel bioreactor.

PMID: 41496216 Liparulo I, Bazhin A, Van Wyhe GK, Gunawan AL, Dadina N, Kwon JH, Schepartz A, Goun E, Stahl A. A clickable CoQ imaging probe reveals that cellular uptake and lysosomal trafficking depend on CD36 and NPC1. Redox Biol. 2026 Feb;89:103936. doi: 10.1016/j.redox.2025.103936.

Ok, away from fun in space, back to Earth. Here comes something new, surprising, and possibly important, once again just because somebody, here colleagues from the US, developed a new tool. This is about a water insoluble molecule (lipid!) in the body named coenzyme Q10 (further referred to as CoQ; a.k.a. as ubiquinon-10. "Ubi" because it is everywhere, from bacteria to elefants to humans). Ten indicates the number of LEGO bricks (isoprene units for connaisseurs) that it is made of. The number varies with the species, mice have Q9, humans have Q10. CoQ works as electron transfer agent in cellular membranes, notably in the mitochondria, the energy converters of the cell. In other places, it is antioxidative, cellular rust protection. The provision of CoQ is comparable to the one of cholesterol. Similar to cholesterol, cells can produce CoQ, and both molecules share parts of the production steps (for pros: mevalonate pathway). And similar to cholesterol, cells can import CoQ via lipoproteins. The study provides first evidence that NPC1 helps CoQ somehow to leave the endosomal-lysosomal system and

to reach its targets in the cell. This may work indirectly, because NPC1 has to remove first cholesterol, before a specific (biology!) but still mysterious transporter can take care of CoQ. In any case: if NPC1 is broken, supply of CoQ goes down, mitos go down, and rust protection fails, so oxidative stress. The extent of damage in a given cell type rises with its depence on interacellular CoQ redistribution by NPC1. In fact, previous studies showed CoQ deficiency in NPCD patients. But treatment with extra CoQ did not help much. The new study may explain why: if NPC1 is broken, external CoQ cannot be properly distributed in cells. How is this in ASMD? Lots of questions and suspense...

Miscellaneous

PMID: 41137896	Panyawechamontri K, Kajiura H, Misaki R, Fujiyama K. Production and purification of tag-free recombinant human acid sphingomyelinase in Nicotiana benthamiana. Plant Cell Rep. 2025 Oct 25;44(11):247. doi: 10.1007/s00299-025-03618-3. PMID: 41137896.

Exam question: What is the connection between ASM and tobacco? So far: *nada*! Correct, until recently. Japanese colleagues managed to produce functional ASM protein in tobacco plants, at least temporarily. And why? Maybe to get tons of vegan enzyme directly from the field?

PMID: 41207335	Kim JM, Kim BY, Kim YH, Yoon HJ, Choi YS, Lee KY, Kim DW, Lee KS, Jin BR. The role of the Niemann-Pick type C2 protein as a sperm-binding protein in honeybees. Insect Biochem Mol Biol. 2026 Jan;186:104443. doi: 10.1016/j.ibmb.2025.

News from South Korea, for honey lovers following up on donkey, pig and prawn breeders! NPC2 is also important for sperm of *Apis mellifera*, the Western honey bee!

Out of the box

This new and "experimental" chapter shall expose from time to time articles of interest unrelated to NPCD or ASMD.

PMID: 39813317 Brandao et al. Inhaled xenon modulates microglia and ameliorates disease in mouse models of amyloidosis and tauopathy. Sci Transl Med. 2025 Jan 15;17(781):eadk3690. doi: 10.1126/scitranslmed.adk3690.

This study tested inhalation of the noble gas xenon as therapeutic approach in mouse models of Alzheimers diseases. It seems to have positive effects through microglial cells.

PMID: 40638739 Wu et al. Microglia replacement halts the progression of microgliopathy in mice and humans. Science. 2025 Jul 10;389(6756):eadr1015. doi: 10.1126/science.adr1015.

This study is also about microglial cells and a rare neurologic disease named ALSP for *adult-onset leukoencephalopathy with axonal spheroids and pigmented glia*. Chinese colleagues report positive effects of bone marrow transplantation in a mouse model and in patients, probably because sick microglial cells were replaced by healthy ones.

PMID: 40945514 Croce et al. A rare genetic variant confers resistance to neurodegeneration across multiple neurological disorders by augmenting selective autophagy. Neuron. 2025 Nov 19;113(22):3780-3797.e7. doi: 10.1016/j.neuron.2025.08.018.

This work is about "natural protection" against neurodegeneration. This comes by a gene with the strange name WDFY3 a.k.a. "Alfy". The encoded protein is involved in autophagy. A specific mutation increases production of the protein and delays onset of Huntington's disease by several years.

PMID: 40945514 Frosch et al. Microglia-neuron crosstalk through Hex-GM2-MGL2 maintains brain homeostasis. Nature. 2025 Oct;646(8086):913-924. doi: 10.1038/s41586-025-09477-y.

An interesting study from Germany is about Sandhoff disease, hexosaminidase B and – again – microglia. the authors show in mouse and patient samples that microglial cells produce lots of hexosaminidase to degrade GM2 and that they deliver the enzyme to neurons. Positive effects were observed after transplantation of healthy bone marrow in HEXB-deficient animals. Following transplantation, healthy microglial cells populate the brain.

PMID: 41068466

Lunke et al. Feasibility, acceptability and clinical outcomes of the BabyScreen+ genomic newborn screening study. Nat Med. 2025 Dec;31(12):4236-4245. doi: 10.1038/s41591-025-03986-z.

A large Australian study shows benefits of newborn screening by genome sequencing. Here, 605 gene with disease-provoking variants were tested in 1000 babies. Sixteen babies at risk were identified compared to only one child identified by standard newborn screening.