

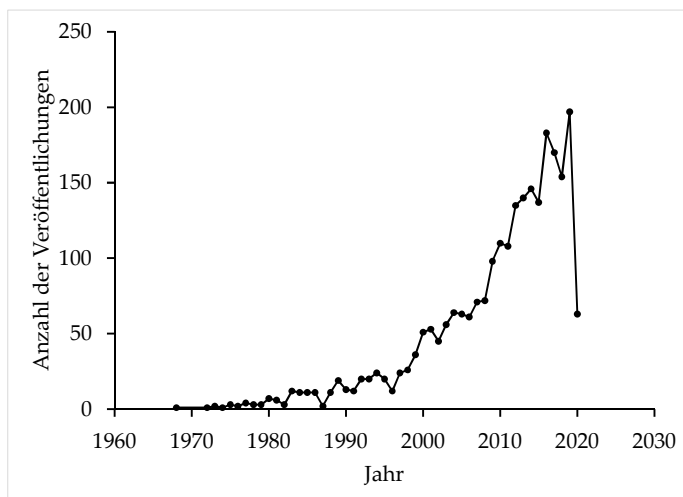
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Dear Readers.

You are looking at the very first issue of my new periodical fresh from the press that aims to inform non-specialists about the latest results of NPC research in a - hopefully regular - manner. The original version was written in German, French and English translations have been accomplished thanks to the support by NPSuisse.

As the title - notably *digest*, not *digestion* - suggests, this is a personal selection, so there is no claim to completeness. Nevertheless, this *digest* is based on "genuine" publications that are listed in the publicly accessible [Pubmed](#) database. The papers mentioned here have been *peer-reviewed*. This means that the results and also their presentation and interpretation have been reviewed anonymously by two, often three experts, who demand corrections and extensions of the work. I have strived to make correct statements, but I cannot guarantee them. My assessments and interpretations are my personal opinion without any claims to validity.

My Pubmed search entailed the following terms: "**niemann pick type c OR niemann pick type C1 OR niemann pick type c2 OR npc1 OR npc2**". I chose the period from January 1st until March 31st 2020 for this issue. The search resulted in a total of **63** scientific publications in various specialized journals. In the following, patient-relevant results will be stated first, followed by studies on animal and cell models and by a "Miscellaneous" chapter. I only mention studies that I can read via my institutional access, some journals and publications are therefore not taken into account. As is customary, the publications are quoted with the first author's surname, the remainder "et al." for more than two authors and the year. I also include the link to the PubMed page.



The figure shows how the number of scientific articles on the subject has developed over the years. The almost exponential growth has become familiar even to laymen - thanks to Covid-19. The figure for 2020 naturally only reflects the publications from January to the start of April.

[Y-axis: Number of publications  
X-axis: Year]

## Patients

<https://www.ncbi.nlm.nih.gov/pubmed/28865947>

Studies by Spanish colleagues (Lopez-de-Frutos et al., 2020) describe new variants of the NPC1 protein, amongst them the case of a 26-year-old NPC patient suffering from neurological and psychiatric symptoms and manifesting a known (p.Ile1061Thr) and an unknown (p.Val856Ala) variant.

<https://www.ncbi.nlm.nih.gov/pubmed/31639880>

With the help of magnetic resonance tomography (MRT), a group from Germany (Gburek-Augustat et al., 2020) showed that NPC patients with varying disease onset, i.e. early/late infantile, juvenile etc., also manifest various changes in certain regions of the brain. This is a further indication that MRT may possibly serve to monitor disease progress in the brain non-invasively - i.e. without an intervention - and to verify possible effects of treatments.

<https://www.ncbi.nlm.nih.gov/pubmed/32033912>

An interesting study (Sidhu et al., 2020) is concerned with the age-old topic biomarkers, i.e. substances that serve diagnosis and monitoring of the patients' condition. Some time ago, a new marker, the so-called LysoSM-509, was presented, it appeared to be a descendant of the famous sphingomyelin, i.e. a component of the cell membrane closely connected with cholesterol. However, the structure of this new molecule remained unknown, which precluded its synthesis and the precise determination of its concentration in the blood. To make a long story short: last year, the structure was clarified and came as a real bombshell: the molecule is a so far unknown "fat" which goes by the name N-palmitoyl-O-phosphocholineserine or in short PPCS. The current study confirms that the PPCS concentration is actually very high in the blood of NPC and possibly also ASMD patients, but not of patients with other disorders or healthy volunteers. Therefore, PPCS is very specific for NP diseases. Moreover, its blood concentration is not influenced by cyclodextrin treatment of the brain (lumbar puncture). Where and how this molecule is precisely produced and what functions it has is not yet clear.

<https://www.ncbi.nlm.nih.gov/pubmed/32138288>

A study by Dardis et al. (2020) summarises the data of all 105 NPC patients known in Italy. The authors emphasise that the number of diagnosed adult patients is increasing, that the normally frequent mutation I1062T is relatively rare and that a large number of differing variants were found instead. At the same time, new variants are being discovered. The study further underlines the impact of genetic factors on symptoms.

<https://www.ncbi.nlm.nih.gov/pubmed/32178982>

A study from the United Kingdom summarises the experience with oxysterol-based diagnosis (Cooper et al., 2020). After five years, the authors come to the conclusion that the test reliably recognises NPC patients, but that also wrongly negative (NPC not recognised) and falsely positive results are possible, as patients with other diseases such as NP A/B and Morbus Wolman likewise show increased values.

<https://www.ncbi.nlm.nih.gov/pubmed/32209649>

An Australian group (Walterfang et al., 2020) shows increased neuro-inflammation in the white substance of the brain in a new PET scan study on adult NPC patients. As reminder, part of the neuro-inflammation, which means really the inflammation reaction in the brain, is activation of so-called microglia cells. Thanks to recent developments, this can be measured via a marker substance that is administered to patients. Cells of the white matter showed stronger activation than those of the grey matter in NPC patients. The white matter mainly entails nerve cables. At the same time, the volume of specific brain areas was reduced, although this did not depend on disease severity. The paper shows once again that imaging methods can be used to assess changes in the brain and possibly the efficacy of treatments - albeit probably only together with other measurements (biomarkers!).

<https://www.ncbi.nlm.nih.gov/pubmed/32222928>

A study that is very pleasing to us comes from Munich. It shows that NPC patients actually manifest pathological changes to the retina (Havla et al., 2020). Our study of the mouse model had already indicated this in 2010. The present work now confirms our prediction: with the help of so-called optical coherence tomography (abbreviated OCT) - it sounds worse than it is - it was shown that certain layers of the retina in NPC patients are thinner than in control volunteers. This non-invasive examination of the retina is therefore possibly - just like the aforementioned PET and MRT - a practicable way to monitor the disease progress and to examine effects of therapeutic drugs.

<https://www.ncbi.nlm.nih.gov/pubmed/32234823>

The same group from Munich also published a study on 20 clinically inconspicuous heterozygous carriers of NPC1 mutations (Bremova-Ertl et al., 2020), which should reveal early indications of neuro-degeneration. In some of the volunteers, the study found conspicuous changes to eye movements, in cognitive tests and in the metabolic activity of certain brain regions, above all the cerebellum.

### **Animal models**

<https://www.ncbi.nlm.nih.gov/pubmed/31312996>

Stephen Turley's group describes a slow accumulation of cholesterol in the small intestine of NPC1-deficient mice (Balb/c Model) (Lopez et al., 2020). This change is weakened by treatment with ezetimibe, which inhibits the cousin of NPC1, the NPC1L1 protein, and by cyclodextrin. The effects of NPC1 malfunction on the small intestine have not been examined very extensively up to now.

<https://www.ncbi.nlm.nih.gov/pubmed/31668555>

A study from the Porter lab is concerned with the important question of why NPC patients show such great differences in the symptoms and disease progress (Cognoux et al., 2020). Whereas genetic factors, i.e. individual differences in the genetic make-up, are high on the list (see elsewhere), there are also environmentally induced candidates. These include pre-natal infections or similar situations that activate the immune system of pregnant women. To test this, NPC1-deficient pregnant mice (nih, Balb/c) were confronted with an agent that

artificially triggers a strong immune reaction, i.e. practically imitates a viral infection. This intervention deteriorates the disease progress in female offspring slightly, but measurably. It remains unclear up to now whether this also applies to humans - the billion-dollar question of transferability of results between animals and humans. In any case, environmentally induced changes remain candidates as disease modifiers.

<https://www.ncbi.nlm.nih.gov/pubmed/31862414>

A study on mice with the so-called nmf164 mutation, which shows a slower disease progress than the NPC1-deficient Balb/c mice (nih allele), confirms a decreased function of mitochondria in the liver (Erickson et al., 2020). Mitochondria guarantee the energy supply to cells and are therefore very important notably for nerve cells which are very energy hungry. The changes affected younger mice in particular. Strangely enough, the malfunction reduced in older age. Maybe the liver is able to counteract this change.

<https://www.ncbi.nlm.nih.gov/pubmed/31937940>

News from the gene therapy front: a group at Harvard University reports on a new approach to repair genetic defects in general. The approach is based on artificial helpers, the so-called base editors. These enzymes, which are based on CRISPR-CAS, can correct the genetic make-up directly, that is to say, for example, replace letters (the bases) (Levy et al., 2020), a kind of Tipp-Ex for DNA. Evidently, these helpers have to be channelled into the cells. A natural carrier is the famous AAV virus. But unfortunately, the DNA carrying the blueprint for the enzymes does not fit into the virus, it is too long. The group was now able to show that the blueprint can be cut in half and distributed onto two viruses. Cells which have been infected with both viruses can then reassemble the enzymes by joining the blueprint halves. Unfortunately, the paper is not yet accessible and is under embargo until June 2020. That happens often in the case of "hot stuff".

<https://www.ncbi.nlm.nih.gov/pubmed/31996359>

A very interesting article from the Pavan lab presents a new mouse model for NPC (Rodriguez-Gil et al., 2020). Above all, it brings further evidence that the disease progress is influenced by genetic factors. The results confirm that the life expectation of mice changes if the same NPC1 mutation is put into various strains of mice. Think of all the variability among dogs, big or small, aggressive or meek. Here too, genetic factors play a role. Naturally, the million dollar question is which factors influence the NPC outcome. Here, the study goes an important step further. It shows firstly that there are a number of places in the genetic make-up which change the lifespan of NPC mice, secondly that these factors are additive and thirdly that they can be found on mouse chromosomes 1, 7 and 17. Now, chromosomes are very long and contain thousands of genes and regulatory stretches. But, identification of these factors and the important proof that and how they change the symptoms of NPC - at least in the mouse model - are now within reach. The necessary experiments are very time-consuming and demand lots of animals, so this will take some time (and money) yet.

### Cells

<https://www.ncbi.nlm.nih.gov/pubmed/31489965>

A study on cell lines examined whether and how sphingomyelin influences the accumulation of cholesterol (Wanikawa et al., 2020). Both lipids accumulate in the cells, but the extent to which the accumulation of one induces that of the other is unclear. A real chicken and egg problem! Note that studies on cell lines are to be treated with caution as their transferability to "normal" cells in a living body is unclear.

<https://www.ncbi.nlm.nih.gov/pubmed/31509197>

A paper from the Balch group shows that a chemical compound named JG98 possibly reverses the accumulation of cholesterol in fibroblasts of NPC patients (Wang et al., 2020). However, this only affects mutations which lead to errors in the folding of the NPC1 protein causing its degradation. JG98 inhibits certain components of the so-called heat-shock protein 70 within the cell and is currently also being tested as a medicine for cancer therapy. Tests are necessary as to whether the substance also works in an animal model or even patients.

<https://www.ncbi.nlm.nih.gov/pubmed/31988149>

A study from Harvard (Feldes et al., 2020) addresses the important question how cyclodextrin reverses the pathological accumulation of cholesterol in cells. There are - as so often - contradictory results on the market. The group refers back to previous studies, amongst them one by us, and follows up the question of whether cyclodextrin triggers the direct release of cholesterol from the cell. As a model, the group uses a cell line - as many others before - and finds that cholesterol is actually released, albeit by a mechanism other than the one that was proposed by previous studies. Now, in principle, diverging results are the daily bread and butter of scientists, and they raise a fundamental issue of biomedical science: does whatever we find in cell cultures also apply to the myriad of specialised cells in living animals and does what we observe in animals also apply to humans? How much confusion is caused by the fact that research is done on unsuited models? Looking for example at the cancer field, the answer is clearly "a lot".

<https://www.ncbi.nlm.nih.gov/pubmed/32072649>

A Danish group (Hede et al., 2020) explored a new approach to correct the genetic defect for Niemann-Pick type C2. As reminder: NPC2 is the "soluble", that means non-membranous, sparring partner of NPC1 and passes cholesterol to the latter. The protein is small compared to NPC1, but it cannot pass the blood-brain barrier. Therefore, a relatively simple substitution therapy cannot function, the same problem as with Niemann-Pick Type A or A/B. The group's idea was to get the cells that form the blood-brain barrier to produce NPC2 and to release it into the brain. The study shows in cell cultures that this may work, but unfortunately the amount of protein is still much too low.

### Miscellaneous

<https://www.ncbi.nlm.nih.gov/pubmed/31711697>

And here is a report fresh from the farm, for pig breeders and other interested parties: a study from Colombia (Valencia et al., 2020) shows that the amount of NPC2 determines the

freezing capacity of pig's sperm: the more, the better. They do not yet know why this is the case, and whether this applies to other animals or humans.

<https://www.ncbi.nlm.nih.gov/pubmed/31940478>

More from the animal kingdom (Takadate et al., 2020): bats, which are known to transmit Ebola and Marburg viruses (and Corona!), manifest differences in the NPC1 protein and these differences determine whether the bat can be infected by a given virus.