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Hearing loss of Niemann Pick type C1 patients: symptom or side effect of the therapy?

According to the definition of MedilinePlus Medical Encyclopedia, "Niemann-Pick disease is a group of diseases passed down through families (inherited) in which fatty substances called lipids collect in the cells of the spleen, liver, and brain.

There are four most commonly recognized forms of the disease: Types A, B, C, and D.

- Types A and B are also called Type I.
- Types C and D are also known as Type II.

Each type involves different organs. It may or may not involve the nervous system and breathing. Each one can cause different symptoms and may occur at different times throughout life." [1]

"Niemann-Pick disease types A and B occur when cells in the body do not have an enzyme called acid sphingomyelinase (ASM). This substance helps break down (metabolize) a fatty substance called sphingomyelin, which is found in every cell in the body. Type A occurs in all races and ethnicities. It is more common in the Ashkenazi (Eastern European) Jew population.

Type C occurs when the body cannot properly break down cholesterol and other fats (lipids). This leads to too much cholesterol in the liver and spleen and too much of other lipids in the brain. Type C is most common among Puerto Ricans of Spanish descent.

Type D involves a defect that interferes with how cholesterol moves between brain cells. It is a variant of type C. This type has only been seen in French Canadian people in Yarmouth County, Nova Scotia." [1]

According to Medline a possible complication of the disease is deafness. About 20% of the patients in NP-C are affected by sensorineural hearing loss and appears to be more frequent in adults. [2] Deafness was observed for 2 among 13 patients with adult form of Nemann Pick type C (NPC) reported by Sevin et al. [3]

HPBCD, as a cholesterol-binding agent was found to be effective in the treatment of NPC disease [4, 5] and received the orphan drug designation by both US and in EU authorities. HPBCD was applied at high doses in various animal models and was found to be safe except hearing loss and toxicity on lungs.

Studying the effect of HPBCD on auditory function using a small number of normal cats and

cats with NPC disease a dose-dependent increase in hearing threshold associated with therapy was found by brain stem auditory evoked response (BAER) testing [6]. The data show that 1000 mg/kg HPBCD had no effect on the BAER response when given weekly for 14 doses between the ages of 3 and 16 wk of age. Doses of 4000 mg/kg body weight resulted in an increase in hearing threshold only after repeated dosing and doses of 8000 mg/kg body weight resulted in significant increases in hearing threshold in both normal cats and cats with NPC disease following the administration of a single dose.

In another study the peripheral auditory function and cochlear histology in mice after subcutaneous injection of HPBCD was studied to test for hearing loss and correlate any observed auditory deficits with histological findings. On average, auditory brainstem response thresholds were elevated at 4, 16, and 32 kHz in mice one week after treatment with 8,000 mg/kg HPBCD. [7] In severely affected mice all outer hair cells were missing in the basal half of the cochlea. In many cases, surviving hair cells in the cochlear apex exhibited abnormal punctate distribution of the motor protein prestin, suggesting long term changes to membrane composition and integrity. Mice given a lower dose of 4,000 mg/kg exhibited hearing loss only after repeated doses, but these threshold shifts were temporary.

National Institutes of Health (NIH) started a study to comprehensively evaluate the auditory phenotype in Niemann-Pick disease, type C1 (NPC1), to understand better the natural history of this complex, heterogeneous disorder, and to define further the baseline auditory deficits associated with NPC1 so that use of potentially ototoxic interventions (e.g., HPBCD) may be more appropriately monitored and understood. [8] Among the fifty patients with NPC1 ranging in age from 4 months to 21 years (mean = 9.3 years) over half of the cohort exhibited hearing loss involving the high frequencies ranging from a slight to moderate degree, and 74% of patients presented with clinically significant hearing loss involving the frequencies most important to speech understanding (0.5, 1, 2, 4 kHz). Despite the heterogeneity of the sample, results among patients were sufficiently consistent to implicate retrocochlear dysfunction in the majority (66%) of individuals, with (22%) or without (44%) accompanying cochlear involvement. Some patients (10%) presented with a profile for auditory neuropathy spectrum disorder. The combination of cross-sectional and longitudinal data indicates these patients are at risk for a progressive decline in auditory function.

These data suggest that hearing loss might be rather the symptom of this severe genetic metabolic disease than the side effect of the therapy.

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Eva Fenyvesi

CycloLab Cyclodextrin R&D Laboratory, Ltd.,

Budapest, HUNGARY

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In vivo Study, Microencapsulation, Oral Drug Delivery, Skin Delivery Model, Transdermal Drug Delivery

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Antiangiogenic, Cells Toxicity, Glycolipids, Neutral Lipids, Phospholipids, Pinus Halepensis Mill.

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Bone Fracture, Bone Metabolism, Osteoporosis, Periodontitis, Statins

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Epilepsy, Intravenous, Lamotrigine, Safety

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Cardiac Regeneration, Growth Factors, Hydrogel, Injectable Scaffold, Stem Cells

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Colon Targeting, Dissolution Methods, Enzymes, Human Faecal Slurries, Polysaccharides, Rat Caecal Contents

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(TRP)V1 Agonists, Drugs-Design, Evodiamine Type Alkaloids, Mass Spectrometry, Quantum Chemistry

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Electrospinning, Nanofibers, Polyvinyl Alcohol (PVA), Silver Nanoparticles (Ag-NP)

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Estradiol, G-1, G-Protein-Coupled Receptor 30, Ovariectomy, Spatial Learning And Memory

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Molecular Modelling, Nanomaterials, Sulfamerazine, TEM

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Anticancer Activity, FTIR-ATR, Job's Plot, Resveratrol, Sulfobutylether-β-Cyclodextrin

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Cell Environmentally Responsive Mechanisms, Controlled-Release Delivery System, Mesoporous Silica Nanoparticles, Responsive Stimuli

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Heptakis(2,6-di-O-methyl)-β-Cyclodextrin, Inclusion Interaction, Molecular Modeling, Prednisolone, Spectroscopic Method, DIMEB

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Drug Delivery, Gene Therapy, Nanomedicine, Nanoparticle, Self-Assembly

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Gene Delivery, Macrophage, Mannose Receptor, Spermine–Mannan

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AFM, Air-Stable Lipid Layer, Force Spectroscopy, Lipid Raft, Spin-Coating

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Biocompatibility, Biodegradable, Dendrimer, Dendritic Polymers, Functionalization, Gene Therapy, Gene Transfection, Gene Vectors

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Biosynthesis, Cholesterol, Hyaluronan, Lipid, Synthase

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Biointerfaces, Biomolecules, Cell-Membrane Models, Surface Functionalization, Thin Nanostructured Films, Vibrational Spectroscopy

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Antioxidants, Caveolae, Heme Oxygenase-1, NRF2, Skin, Stress Proteins, 4-Hydroxynonenal, Lipid Peroxidation, Methyl-β-Cyclodextrin, RAMEB

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Cholesterol, Endocytosis, GB3, Glycosphingolipids, Golgi, Sphingomyelin

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Boar, Holding Time, Post-Thaw Incubation Temperature, Spermatozoa, Thawing Rate

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Acidic Compartment, Autophagy, Cholesterol, Neurons, Niemann–Pick Type C

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GLP-1, Linoleic Acid, Lipids, Serotonin

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Apoptosis, Cancer Therapy, Cholesterol, Growth Factor Receptor Signaling, Membrane Rafts, Neoplasia

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Gene-Silencing, RNA Interference, RNAi Delivery, Therapeutics

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Canonical Transient Receptor Potential 6 (TRPC6), Fluorescence Resonance Energy Transfer (FRET), Intracellular Tension, Lipid Rafts, Mechanical Microenvironment

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Autophagosome, Baculovirus, Endosomal Fusion, Intracellular Trafficking, Microtubule

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Degradable, Gene Delivery, Pasp, Pdmaema, Ring-Opening Polymerization

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Barrier Properties, Controlled Release System, MFC-Coated Paper, Microfibrillated Cellulose, Nanoporous Network

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Branched Limited Dextrin, DSC, Molecular Dynamic Simulation, Starch Retrogradation, X-Ray Diffraction

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Adsorption Characteristics, Adsorption Isotherm, Adsorption Kinetics, Debittering, Macroporous Resins, Ponkan Juice

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MCPA, Phenoxyacetic Acid Herbicides Phase Solubility Study

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Anthocyanins, Color Stability, Encapsulation, Freeze Drying, Saffron Petal

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Microencapsulation, Spray Drying, Sunflower Oil, Vegetable Oil

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Archaea, Goat, Methane, Propyl Propane Thiosulfinate, Rumen, $\mathcal{A}$-Cyclodextrin-Propyl Propane Thiosulfinate Complex, in vitro Culture of Methanogens

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Aseptic Packaged, Physic-Chemical Analysis, Sensory Analysis, Soymilk, Ultra High Pressure Homogenization (UHPH)

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Enzymatic Modification, Organoleptic Properties, Steviol Glycosides, Stevioside, α-Amylase

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Flavor Inclusion Complex, Kinetics, Pyrolysis, Thermodynamics, Thermogravimetric Analysis, Aggregates

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Bioavailability, DDT, Earthworms, Soil, Thin-Film Solid-Phase Extraction (TF-SPE)

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Antioxidant Properties, Grapevine Waste, Green Extraction, Hazelnut Skin, Polyphenols

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Availability, Biochar, PAHs, Sewage Sludge

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Fenton, Hexachlorocyclohexanes, Lindane, Oxidation, Persulfate, Soil

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COD, Ethyl Violet Dye, Photocatalytic Decoloration, TiO2

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Adsorption, Arsenic, Chitosan, Nanocomposite, Removal, Zero Valent Iron, CMβCD

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Poly(N-Isopropylacrylamide), Polyethylene Glycol, Polyvinyl Alcohol, Polyvinylpyrrolidone, Water-Soluble Polymer

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Carbamazepine, Fe-NTA Complexes, Fenton-Like Reaction, Nano-Fe3O4, Nitrilotriacetic Acid

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Electrocatalyst, Graphene, Methanol Oxidation, Pt Nanoparticles

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Adsorption, Cellulose, Esterification, Functionalization, Methyl Violet

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Chemical and Photochemical Reactions, Pseudophase Model, Restricted Geometry Conditions

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Environmental Matrices, Extraction, Fluorescence, Humic Substances, Natural Organic Matter, Polycyclic Aromatic Hydrocarbon

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Methylene Blue, 4-Chlorophenol Species, Reactive Oxygen

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Hydroxybenzoic Acid, Magnetic Separation, Molecularly Imprinted Polymers, Water Sample

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Controlled/Living Radical Precipitation Polymerization, Molecularly Imprinted Polymers, Water-Compatible

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Azobenzene, Membrane, Permeability, Photo-Responsibility, Poly (Ether Sulfone)

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Cyclodextrin Pseudo-Polyrotaxanes, Molecularly Imprinted Polymer, Polyvinyl Alcohol, Protein Adsorption, Pseudo-Supports

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Microbial Activity, OCPS-Contaminated Site, Portulaca Oleracea L. Cultivation, Soil Washing, DDTs, Endosulfans, 1,2,3,4,5,6-Hexachlorocyclohexanes, Heptachlors, Chlordanes

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Electrokinetics, IGEPAL CA-720, Persulfate, Polychlorinated Biphenyls, Soil Remediation, Zero-Valent Iron

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Micellar Electrokinetic Chromatography, Monolithic Capillary Electrochromatography, Polycyclic Aromatic Hydrocarbons

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Capillary Zone Electrophoresis, Complexation, Dual Selector System, Model of Electromigration, Heptakis(2,6-di-O-methyl)-β-CD, 6-O-A-Maltosyl-β-CD, Ibuprofen, Flurbiprofen

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Capillary Electrophoresis, Migration, Mobility, Nonaqueous, Organic Solvents, pKa Value

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Adenosine Triphosphate, Aptasensor, Electrochemiluminescence, Host–Guest Recognition, Metallocyclodextrin, Tris(Bipyridine)Ruthenium(Ii)-B-Cyclodextrin

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Cyclic Voltammetry, Differential Pulse Voltammetry, Electrochemical Impedance Spectroscopy, Isoorientin, K10 Montmorillonite, β-Cyclodextrin

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Bupropion, (2-Hydroxy)propyl-γ-cyclodextrin, Inclusion, Pharmaceutical Preparations, Spectroscopy

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Bioimaging In Vivo, Lanthanide, Multi-Modality, Upconversion Luminescence, Upconversion Nanophosphors

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AMP/ADP/ATP, Anthracene, Fluorescence Titration, Sensor

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Cobalt, Iron, Lanthanide, MR Imaging, Manganese, Oxidation, Reduction

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Chiral Separation, Diketopiperazine, Pheromone, Supercritical Fluid Chromatography

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Cyclic Voltammetry, Dopamine, Dopamine Sensor, Supramolecular System

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Chemosensors, Colorimetry, Coordination Complexes, Dye-Metal Complexes, Dyes, Naked-Eye Detection.

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Autoimmune, Combinatorial Glycomic, Cholesterol, Galactocerebroside

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2/3-Chlorophenol, Electrochemical Sensor, Graphene, Simultaneous Determination

Sensors and Actuators B: Chemical, 2014, 195, 452–458; DOI:10.1016/j.snb.2014.01.035

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Homepage:www.cyclolab.hu
H-1525 P.O. 435, Budapest, Hungary
Tel:(361) 347-6060
Fax: (361) 347-6068
e-mail: cyclolab@cyclolab.hu