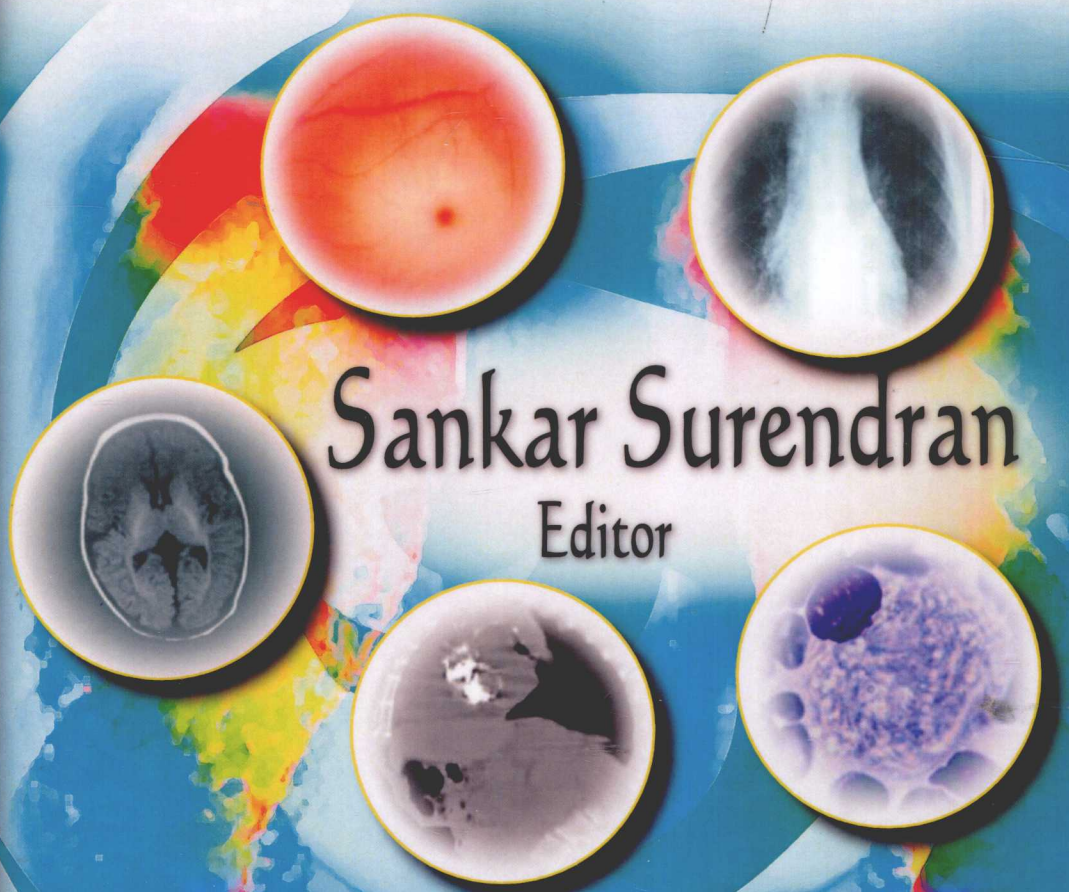
Neurochemistry of Metabolic Diseases

Lysosomal Storage Diseases, Phenylketonuria and Canavan Disease



Sankar Surendran
Editor

Metabolic Diseases - Laboratory and Clinical Research

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METABOLIC DISEASES - LABORATORY AND CLINICAL RESEARCH

NEUROCHEMISTRY OF METABOLIC DISEASES

LYSOSOMAL STORAGE DISEASES, PHENYLKETONURIA AND CANAVAN DISEASE

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Nova Science Publishers, Inc.
New York

Library of Congress Cataloging-in-Publication Data

Neurochemistry of metabolic diseases : lysosomal storage diseases, phenylketonuria, and Canavan disease / editor, Sankar Surendran.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-61209-671-1 (hardcover)
1. Brain--Metabolism--Disorders--Pathophysiology. 2. Brain--Metabolism--Disorders--Treatment. I. Surendran, Sankar. II. Title.
[DNLM: 1. Brain Diseases, Metabolic, Inborn--physiopathology. 2. Brain Diseases, Metabolic, Inborn--therapy. WL 350]

RC365.N44 2011
616.8'3--dc22

2011007138

Published by Nova Science Publishers, Inc.† New York

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Preface

Metabolic disorder is caused by a gene defect, environmental factors or an unknown etiology. Altered metabolism caused by these factors affects normal function of various organs including the brain and may lead to abnormal phenotype. Understanding agents of causing these abnormalities is useful to interpret possible targets in these diseases. This book reveals what factors contribute in lysosomal storage diseases, Phenylketonuria and Canavan disease, as they are major emerging diseases in multiethnic populations.

Chapter 1 - Sialidosis is a rare lysosomal storage disorder caused by a malfunction of the enzyme sialidase (neuraminidase). This enzyme defect results in intracellular storage of sugar-like substances, called sialic acids. The corresponding gene NEU1, which is mutated in sialidosis, is located on the short arm of chromosome 6 (6p21.3). In humans, there are two forms of sialidosis: the milder type I (ST-1) which develops in adolescence or early adulthood and the more severe type II (ST-2) which presents at birth or in infancy. So far, no specific treatment for this progressive disease is available. This chapter provides up to date information on the enzyme sialidase and its substrate sialic acid, the relevant genetic background, the different subgroups of sialidosis including their clinical management, and other inherited conditions involving the sialic acid metabolism (galactosialidosis, sialuria and sialic acid storage disease).

Chapter 2 - Gaucher disease, the most prevalent glycolipid storage disorder, has been treated with Enzyme Replacement Therapy (ERT) using the current gold standard, recombinant imiglucerase (Cerezyme®; Genzyme Corporation), for more than 15 years. Based on clinical data from thousands of patients world-wide, it can be said that within 2-5 years, most patients will experience improvement in hemoglobin and platelets, reduction in spleen and liver volumes, improved bone density, and in children in linear growth, as well as reduction in surrogate markers such as chitotriosidase/CCL18 levels. Nonetheless, there are currently unmet clinical goals such as preventing progression of neuronopathic disease, some forms of pulmonary pathology, and skeletal involvement in those at risk for these manifestations. Shire Human Genetics Therapies has recently received FDA approval for ERT with velaglucerase alfa (VPRIV™) and Protalix Pharmaceuticals has successfully completed Phase 3 trials with its plant-derived enzyme, taliglucerase alfa (UPLYSO™). Both of these drugs are available via compassionate access programs because of supply shortages of imiglucerase which began mid-2009. Substrate reduction therapy (SRT) with the glucose-analogue, miglustat (Zavesca®; Actelion Pharmaceuticals), because of its more problematic

safety profile, was approved with a caveat for adults for whom ERT is not appropriate. A ceramide analog SRT (eliglustat; Genzyme Corporation) is currently in clinical trials. Pharmacological chaperones are also currently being tested. Nonetheless, none of these are curative and most symptomatic patients will also require ancillary treatments, most notably, orthopedic surgery.

Chapter 3 - Parkinson's disease (PD) is a neurodegenerative disorder thought to be caused by oxidative stress and characterized by reduced levels of catecholamines. The cardinal signs are tremor, rigidity, bradykinesia, and postural instability. Oxidative stress plays a key role in neurodegeneration and the motor abnormalities seen in PD. Altered levels of proteins caused by these changes lead to dysfunction of the ubiquitin-proteasome pathway. Glucocerebrosidase deficiency is involved in sporadic Parkinson's disease and also in Gaucher disease, a lysosomal storage disease. Recent studies suggest that herbal medicines may facilitate molecular changes that improve motor function in PD.

Chapter 4 - Ataxia-telangiectasia mutated (ATM) is a DNA repair protein. Defect in the gene resulting protein deficiency leads to symptoms including lysosome accumulation, neurodegeneration and cancer, a disease known as Ataxia-telangiectasia (A-T). The syndrome in the disease includes progressive cerebellar ataxia, dysarthric speech, oculomotor apraxia, choreoathetosis and oculocutaneous telangiectasia. Studies performed in ATM-deficient mice revealed increased levels of nitric oxide-mediated damage, increased ROS and reduced catalase activity in neural cells. In contrast to the nuclear localization of ATM protein observed in cultured cells, ATM protein is predominantly cytoplasmic in Purkinje cells and other neurons. No curative strategy for A-T patients exists. Although AT is not a metabolic disorder, since ATM deficiency leads to lysosomal accumulation, the review was aimed to understand ATM deficiency resulting abnormalities and this is the subject of this review.

Chapter 5 - Rett syndrome is characterized by early neurological regression that severely affects motor, cognitive and communication skills, leading to microcephaly, a delay in acquiring new skills, absence of speech, emergence of autistic features, loss of purposeful manipulation skills, replaced by stereotyped hand movements, other motor abnormalities including abnormal muscle tone, ataxia and apraxia, and often a seizure disorder. It is a monogenic X-linked dominant disorder due to mutations in *MECP2*, that encodes the methyl-CpG binding protein MeCP2. There are several mouse models either based on conditional knocking out of the *MeCp2* gene or on a truncating mutation. Perspectives in altering gene expression are discussed alongside with perspectives in clinical management.

Chapter 6 - Krabbe disease is a rare inherited neurodegenerative disease which affects both the central and peripheral nervous system. The disease is caused by a deficiency of the lysosomal enzyme galactocerebrosidase which leads to the inability to degrade galactosylceramidase and galactosylsphingosine. The incidence of the disease in the United States is reportedly 1/100,000 with 90% of affected patients having the early infantile phenotype. (These figures, however, have been brought into question with the advent of population based newborn screening.) In addition to the invariably fatal early infantile phenotype, there are the late infantile, later onset, adolescent and adult phenotypes, which have different clinical manifestations and disease courses. Moreover, there is wide phenotypic variability within families, especially in the later onset, adolescent and adult phenotypes. The sole available treatment for the disease is hematopoietic stem cell transplantation which has both significant morbidity and 10% mortality and is only effective if performed prior to the onset of symptoms. Transplanted presymptomatic children with the early infantile phenotype

have significantly longer survivals than untreated children but the majority develops motor and language abnormalities. Newborn screening for the disease began in New York State in August 2006 in part to identify those presymptomatic infants who might benefit from transplant. The major issue with the screening process has been that since neither the level of GALC activity nor the genotype (with limited exceptions) reliably predict phenotype, it has been difficult to identify with certainty which children will develop the early infantile phenotype and should be considered for emergent transplantation as opposed to those with later onset, adolescent and adult variants who may not become symptomatic for many years.

Chapter 7 - Gangliosidoses are two groups of genetic diseases with excessive accumulation of gangliosides. G_{M2}-gangliosidosis is defined as a group of β-hexosaminidase deficiency disorders, causing excessive storage of ganglioside G_{M2}, mainly in the central nervous system. The enzyme consists of two subunits encoded by two genes *HEXA* and *HEXB*, respectively. Two isoenzymes are present in somatic cells, Hex A, consisting of α and β subunits, and Hex B, consisting of two β subunits. Another protein cofactor is necessary for degradation of the substrate: G_{M2} activator encoded by the gene *GM2A*. G_{M1}-gangliosidosis is a group of β-galactosidase deficiency disorders, causing excessive storage of ganglioside G_{M1}, oligosaccharaides and a mucopolysaccharide keratan sulfate in the central nervous system and other non-neural tissues. Mutations of the gene *GBL1* result in loss of β-galactosidase activity and a variety of phenotypic expressions with or without brain damage mainly in children. Mutations of another lysosomal protein, protective protein/cathepsin A, regulating expression of β-galactosidase activity, cause another disease galactosialidosis, with combined deficiency of β-galactosidase, neuraminidase and cathepsin A. Pathogenesis of these two gangliosidoses has been extensively investigated. Single enzyme deficiency will cause a variety of molecular effects in somatic cells. Understanding of these complicated molecular events will provide information for development of new therapeutic approaches. At present substrate reduction therapy and chaperone therapy have been proposed and tried for the brain damage in gangliosidoses.

Chapter 8 - Therapies for lysosomal storage disorders (LSDs) have been developed clinically and experimentally. These include hematopoietic stem cell therapy (HSCT), enzyme replacement therapy (ERT), and gene therapy, all of which lead to the partial restortion of enzyme activity. Substrate reduction therapy (SRT) and the use of pharmacological chaperones have also been attempted. Although HSCT is not entirely effective, impairment of cognitive function has been prevented if the patients are treated at an early stage. However, HSCT still brings concerns because of the high morbidity and mortality rates. Gene therapy is still experimental at this moment. SRT is orally administered and clinical assessment is under investigation.

Treating LSDs with ERT relies on the cellular uptake of exogenous enzyme by receptor-mediated endocytosis. ERT using macrophage-targeted recombinant β-glucocerebrosidase is successful in treating the nonneuronopathic form of Gaucher disease, which opened the door to the development of this treatment for further LSDs. ERT was also approved for use in patients with Fabry and Pompe diseases, mucopolysaccharidosis I (MPS I), MPS II, and MPS VI. Patients treated with ERT had clinical improvement of somatic manifestations and improved quality of life. However, there are several limitations with current regular ERT: 1) immunological issues (raising the antibody level leads to reduced efficacy), 2) rapid clearance

from blood circulation, 3) limited effect on neurological and skeletal symptoms, 4) high cost, and 5) lifelong dependence on weekly infusions.

Thus, in spite of substantial success of ERT, no curative therapies exist for LSDs, especially with bone dysplasia and central nervous system (CNS) involvement. Supportive measures are also used to treat the clinical manifestations of LSDs. Medications are used for palliative care, such as non-steroidal anti-inflammatory drugs for joint pain, antibiotics for pulmonary infections and oxygen supplementation for pulmonary compromise. Surgical interventions such as cervical fusion, spinal cord decompression, osteotomy, and hip replacement are often required.

In this chapter we describe the efficacy of ERT and its limitations in comparison with other therapeutic options available for a particular group of LSDs, The Mucopolysaccharidoses (MPS).

Chapter 9 - Lysosomal storage diseases (LSDs) are caused by inborn error genetic defects and most affected babies show pathology in the CNS. LSDs are caused by a specific inherited enzyme deficiency that results in accumulation of substrates in the lysosomes, distension of the organelles and subsequent cellular malfunction. Currently, no effective treatment is available for most of the LSDs, because the blood–brain barrier bars entry of enzyme preparations into the brain. Treatment for LSDs can be divided into those address symptoms or those address cause. At present, successful treatments for the LSDs are enzyme replacement therapy (ERT) and cell therapy. ERT is most successful in Gaucher disease and has been approved for Fabry disease, Pompe disease and mucopolysaccharidosis I, II, VI (MPS I, II, VI). In addition, ERT for MPS IIIA and IVA are being tested. Limitations in ERT include need for life-long treatment, development of antibodies, and inability to cross blood brain barrier (BBB) resulting in failure to halt disease progression in the brain. Transplantation of hematopoietic stem cells (HSCs), bone marrow stem cells (BMSCs) and umbilical cord-derived stem cells (UCSCs) offer effective but limited efficacy for patients suffering from Krabbe disease, MPS VII and adrenoleukodystrophy but in other LSDs they are ineffective. Intracranial/intracerebral transplantation of genetically modified stem cells as enzyme delivery system could bypass the BBB effectively and ensure release of therapeutically beneficial amount of enzymes to affected CNS lesion sites. For this reason, stem cell-based gene therapy is the most effective treatment for LSDs. In mouse models of MPS VII, Krabbe disease, Tay-Sachs disease, Nieman Pick A disease and Sandoff disease, genetically modified neural stem cells (NSCs) encoding enzyme genes effectively decreased lysosomal storage, reduced pathology and extended life span of animals. Cell-based gene therapies for LSDs bridge the application of ERT and gene therapy and are important direction to pursue in the future.

Chapter 10 - A biomarker is an analyte that indicates the presence of a biological process linked to the clinical manifestations and outcome of a particular disease. In the case of lysosomal storage disorders (LSDs), accumulating metabolites and their secondary products or proteins specifically secreted by storage cells are good candidates for biomarkers. Clinical applications of biomarkers are found in improved diagnosis, monitoring of disease progression and assessment of therapeutic correction. In this chapter, these applications are illustrated by reviewing the discovery and use of biomarkers for Gaucher disease and Fabry disease.

Chapter 11 - Phenylketonuria (PKU) is the most common inherited metabolic disease in Turkey (1:5049). Turkey has a particularly high incidence of PKU compared with other

countries; this includes a high number of late-diagnosed patients, probably due to the relatively recent availability of screening (since 1986) and treatment. Occurrence of consanguineous marriages might partially be responsible for the high incidence of PKU. PKU is treatable by a low phenylalanine diet for life. It is clear that in our country public and health staff's awareness in rural provinces is not at the desired level, as evidenced by the findings that 26.6% of families have more than one affected child, which could have been prevented by proper counselling. The Turkish Society for the Screening and Treatment of PKU, established in 1986, focuses on the educational activities to inform the medical staff and the public through the media. An epidemiological and clinical overview of PKU is given in this chapter together with an account for newborn screening, prenatal diagnosis and dietary treatment.

Chapter 12 - Phenylketonuria (PKU) is an inborn error of amino acid metabolism caused by mutations in the phenylalanine hydroxylase (PAH) enzyme resulting in the inability to convert phenylalanine (phe) to tyrosine. If untreated, PKU causes irreversible cognitive impairment with accumulation of phe in the brain. When diagnosed and treated from birth with a low phe diet, individuals with PKU grow and develop normally. Adherence to the low-phe PKU diet is recommended lifelong, however it is extremely challenging to follow and compliance is known to decrease with age, the consequences of which range from headaches to the devastating effects of Maternal PKU. Current research is investigating the neurological manifestations of early treated PKU by examining not only structural and neurochemical features, but functional differences in executive function as well. Due to the challenges of dietary treatment, new options are needed to improve metabolic control and outcomes. Some of these new treatment options include tetrahydrobiopterin (BH_4) therapy, supplementation of large neutral amino acids (LNAA), a new dietary paradigm using the intact protein glycomacropeptide (GMP), and therapy using pegylated phenylalanine ammonia-lyase (Peg-PAL). The growing population of adults with early treated PKU offers an opportunity to further understand the genetics, chronic complications and discover ways to address the dietary challenges of PKU.

Chapter 13 - Canavan disease (CD) is an autosomal recessive neurodegenerative disorder. Elevated levels of N-acetylaspartic acid (NAA) and aspartoacylase (ASPA) mutation(s) were observed in patients with CD. Recent studies on CD around the globe suggest that CD phenotype is complex and CD is not restricted only to homozygosity of the *ASPA* gene. Patients with severe form show symptoms which include prominent macrocephaly, hypotonia and mental retardation.

Patients with mild form show slightly increased head size and mild elevation of urinary NAA. N-acetylaspartic acid induced nitric oxide (NO) toxicity mainly via inducible nitric oxide synthase (iNOS) to lead genotoxicity and protein interaction. Neurons affected in the brain of CD include caudate putamen, periaqueductal gray matter, pons, thalamus, globus pallidus and corpus callosum. Osteoporosis is one of the events in CD. Cell therapy is one of the important approaches to replace the lost cells and the lost enzyme in CD.

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In: Neurochemistry of Metabolic Diseases
Editor: Sankar Surendran, pp. 1-14

ISBN 978-1-61209-671-1

Chapter I

Sialidosis: Pathophysiology and Therapeutic Approaches

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Abstract

Sialidosis is a rare lysosomal storage disorder caused by a malfunction of the enzyme sialidase (neuraminidase). This enzyme defect results in intracellular storage of sugar-like substances, called sialic acids. The corresponding gene NEU1, which is mutated in sialidosis, is located on the short arm of chromosome 6 (6p21.3). In humans, there are two forms of sialidosis: the milder type I (ST-1) which develops in adolescence or early adulthood and the more severe type II (ST-2) which presents at birth or in infancy. So far, no specific treatment for this progressive disease is available. This chapter provides up to date information on the enzyme sialidase and its substrate sialic acid, the relevant genetic background, the different subgroups of sialidosis including their clinical management, and other inherited conditions involving the sialic acid metabolism (galactosialidosis, sialuria and sialic acid storage disease).

1. Sialic Acid

Sialic acids (Sias) are a diverse group of ca. 50 monosaccharides which are characterized by a 9-carbon backbone and which are widely distributed in living organisms (Figure 1) [1]. Their name was coined by Blix et al. in 1957 and is derived from the Greek word 'sialos' meaning 'saliva' as they were first detected in salivary gland secretions (mucins).

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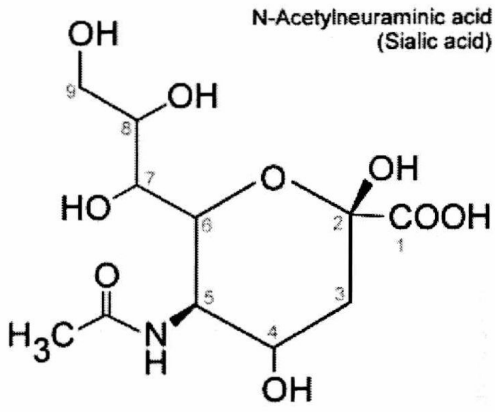

Figure 1. Structural formula of 5-acetamido-2-keto-3,5-dideoxy-D-glycero-D-galactononic acid (Neu5Ac, $C_{11}H_{19}NO_9$; reprinted from [1] with kind permission of Christian Thorsten).

Sialic acids form terminal glycosidic bonds with glycans (oligosaccharides and polysaccharides), proteoglycans (glycoproteins) and gangliosides (glycolipids). These negatively charged sialylglycoconjugates are frequently attached to cellular and subcellular membranes where they have a protective, stabilizing or binding function [2]. For example, influenza A virus hemagglutinin, which belongs to the lectin family, recognizes sialic acid residues on host cell surfaces thus enabling the virus to enter the cell [3]. Sialic acid containing gangliosides have also been shown to act as binding site for the neurotoxin TeNT produced by the bacterium Clostridium tetani [4]. Recent research suggests that N-acetylneuraminic acid has a reducing (antioxidative) effect on hydroperoxides [5]. Most sialic acids are derivatives of N-acetylneuraminic acid or 2-keto-3-deoxynononic acid (Kdn), both of which are synthesized from hexose molecules. The enzyme glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE) converts UDP-N-acetylglucosamine to N-acetylmannosamine-6-phosphate and UDP. Condensation of ManNAc-6-P with phosphoenolpyruvic acid results in sialic acid 9-phosphate, which is dephosphorylated to free sialic acid. Neu5Ac is then transported into the nucleus, activated to CMP-Neu5Ac with CMP-sialic acid synthetase (CMAS), and released back into the cytoplasm. There and in the Golgi apparatus, activated Sias are modified with hydroxylases and linked to new glycoconjugates with transferases.

In mammalian cells degradation of sialylated macromolecules takes place in the lysosome. Sialic acid molecules are removed from glycoconjugates with sialidases and delivered to the cytoplasm via the lysosomal transmembrane protein sialin (OMIM 604322). In the cytoplasm the Sias are either recycled or metabolized to N-acetyl-mannosamine and pyruvic acid catalyzed by pyruvate lyases [2, 6].

2. Sialidase

The enzyme exo-alpha-sialidase (neuraminidase, EC 3.2.1.18, OMIM 608272) cleaves terminal sialic acid residues from glycans, glycoproteins and glycolipids. The related endo-alpha-sialidase (EC 3.2.1.129) catalyzes endohydrolysis between sialic acid molecules. The database Swiss-Prot lists several hundred proteins belonging to the superfamily of

neuraminidases, which have been isolated from various organisms (Figure 2) [7, 8]. These enzymes can be found in lysosomes, mitochondria, cytoplasm and plasma membrane. It is well known that viral neuraminidase accelerates the entry of influenza virus into a host cell and facilitates the release of newly formed virions [9, 10]. This process can be hindered by the neuraminidase inhibitors oseltamivir and zanamivir which have been shown to reduce the complication rate of influenza virus infections in humans [11, 12].

So far four types of human neuraminidase have been identified (NEU 1 - 4). NEU1 is the only one to be expressed in all organ tissues. Lysosomal sialidase is encoded by the NEU1 gene (6 exons, 5 introns) on chromosome 6p21.3 and consists of 415 amino acids (MW ~ 45.5 kDa). It is part of a multienzyme complex that includes β-galactosidase (EC 3.2.1.23), protective protein/cathepsin A (PPCA or CTSA) and possibly N-acetylgalactosamine-6-sulfatase (EC 3.1.6.4) [13, 14]. Apart from assisting with the degradation of sialoglycoconjugates in lysosomes, sialidases have a variety of other functions which are still emerging. They regulate lysosomal exocytosis [15], influence the production of interferon-gamma [16], suppress the metastasis of cancer cells [17] and modify the properties of cervical mucus [18], to name but a few.

Figure 2. Molecular structure of the neuraminidase of influenza virus A (in nature the molecule occurs as a tetramer (reprinted from Protein Data Bank 1nn2) [8].

3. Sialidosis

Sialidosis (OMIM 256550) is one of over 40 autosomal recessive lysosomal storage disorders (LSDs) and has an incidence/prevalence of ca. 1 in 4.2 million [19]. It is caused by

a deficiency of the lysosomal enzyme sialidase which leads to intralysosomal accumulation of sialylated macromolecules [20].

3.1. History

In 1968 Spranger et al described two boys with developmental delay, coarse facies, skeletal anomalies and vacuolated lymphocytes, hepatocytes and bone marrow storage cells. Acid mucopolysaccharides in the urine were normal but mucoprotein-mucopolysaccharide complexes (e.g. hexosamine) were increased. One patient had an ocular cherry-red spot and developed seizures.

Along with other literature reports they classified these cases as an intermediate group between the mucopolysaccharidoses and the sphingolipidoses, and called it 'lipomucopolysacharidosis' [21]. The name was subsequently changed to mucolipidosis type I. Evaluation of further similar patients revealed increased amounts of bound sialic acid in urine and cultured fibroblasts, and decreased activity of neuraminidase [22, 23]. O'Brien and colleagues described four young adults with cherry-red macular spots, slowly progressing myoclonus and visual impairment, and near-normal intelligence. Urine analysis demonstrated high concentrations of sialyloligosaccharides, and fibroblast assays revealed reduced acid neuraminidase activity.

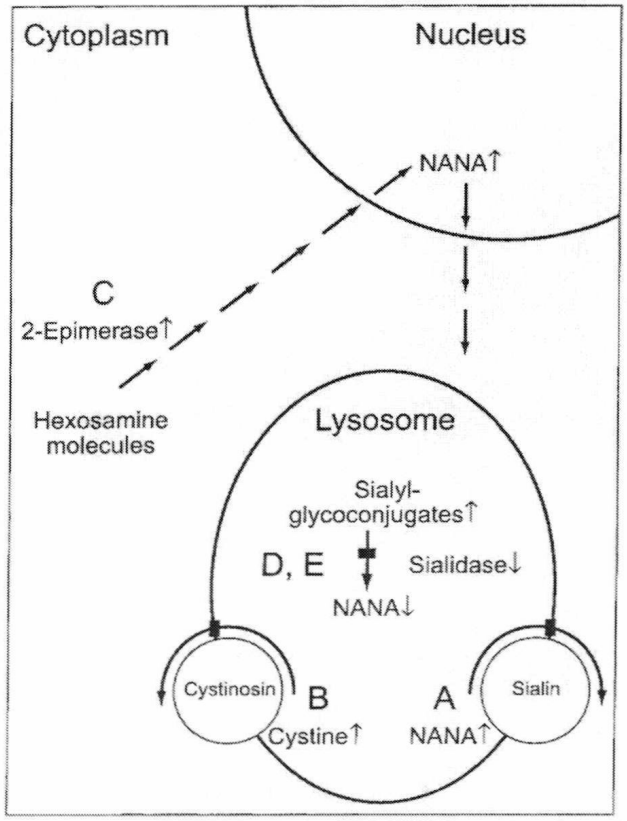

Figure 3. Sialidosis. Schematic representation of the metabolic pathways in (a) sialic acid storage disease; (b) cystinosis; (c) sialuria; (d) sialidosis; (e) galactosialidosis (NANA, N-acetylneuraminic acid; 2-epimerase, uridine diphosphate N-acetylglucosamine 2-epimerase; reprinted from [2] with kind permission of Mary Ann Liebert, Inc., publishers).

They used the term cherry red spot-myoclonus syndrome for this condition and recognized overlapping features with mucolipidosis I. They concluded that these two diseases were allelic and that the phenotypic variations could be explained by differences in the residual enzyme activity, with mucolipidosis I being the more severe form [24, 25]. Lowden and O'Brien reviewed 37 literature cases of human neuraminidase deficiency and divided them in sialidosis type I and type II [26].

In 1971 Goldberg et al reported three children of a Mexican family who had a coarse facies, developmental delay, epilepsy and skeletal anomalies. Two of them were extensively investigated [27]. Vacuolated Kupffer cells (macrophages) were seen on liver biopsy specimens, and β-galactosidase activity was low compared to controls in samples of skin and conjunctiva. This new syndrome resembled the mucopolysacharidoses, mucolipidoses and sphingolipidoses, and was later identified as galactosialidosis, a condition closely related to sialidosis (Figure 3) [2].

3.2. Sialidosis Type I (ST-1)

Sialidosis type I or normosomatic type, also called cherry-red-spot-myoclonus syndrome, is the milder of the two forms of sialidosis. It is a slowly progressing condition and usually presents in the second or third decade of life [28]. Typical features are visual impairment, cherry-red ocular spots, nystagmus, myoclonus, seizures, ataxia and dysarthria. Intellectual abilities are frequently normal (Figure 4) [29, 30, 31].

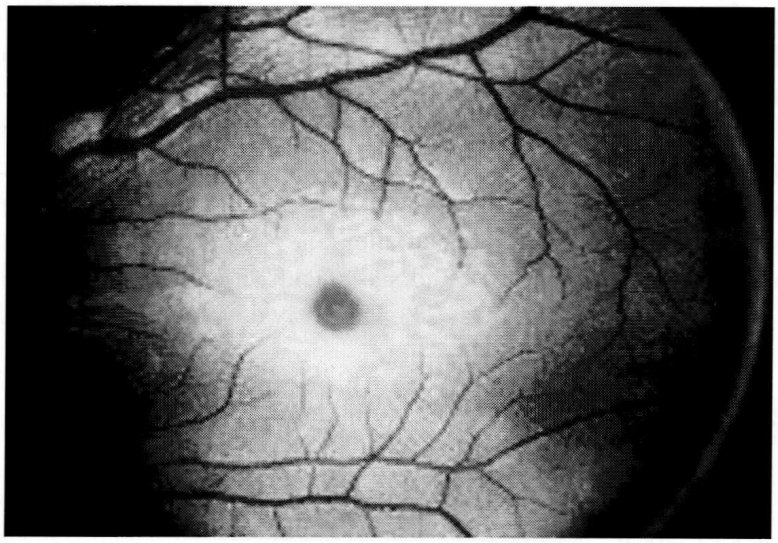

Figure 4. Example of a cherry-red macular spot as seen in sialidosis and other lysosomal storage diseases (reprinted from [31] by permission).

An early description of two affected siblings is given by Durand et al. [32]. A 22-year old male mechanic was investigated because of decreasing visual acuity. On examination he was found to have bilateral cherry-red macular spots, corneal opacities, color blindness and hyperreflexia. His 13-year old sister also had a visual deficit and hyperreflexia, and in addition slight coordination difficulties and hepatomegaly.