Niemann Pick Type C-Case Report

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Abstract

Niemann-Pick disease is an autosomal recessive lipid storage disease, characterized with differentiating levels of hepatosplenomegaly and progressive psychomotor retardation. Disease emerges with early childhood ataxia and progressive dementia, and the most evident features are early childhood hepatosplenomegaly, vertical supranuclear ophthalmoplegia, ataxia, dysarthria, mental-motor retardation, and seizures.

In this report, we present our uncooperative 5-year old female patient MD from Kumanovo, with hepatosplenomegaly, mental-motor retardation, developmental retardation, deglutition, speech deficiency, ataxia and seizures, who was admitted to our clinic. The genetic testing and diagnosis was done at the Tokuda Clinical Hospital in Sofia, Bulgaria.

In accordance with the age of the child in her mouth, all primary teeth were present, and extensive lesions with dental caries were observed in the primary molars. At the first arrival of our clinic extraction of the first upper primary incisions was done with the local anesthesia (Lidocaine spray). It was not possible to perform X-ray of the teeth. The child was placed on the waiting list for dental treatment under general anesthesia.

Early diagnosis results in improved quality of life for the patient. The early adoption of preventive measures is important to reduce and control the risk of caries activity. Preventive measures, education, caregiver training, and frequent consultations with pediatric dentist are essential for patients with special health care needs.

Key Words: Niemann-pick disease, Type C, Anesthesia

Introduction

A rare disease, sometimes known as a disease that is not common. Orphan disease is a disease which has not been “adopted” by the pharmaceutical industry because it provides little financial incentive for the private sector to make and market new medications to treat or prevent it. 1 of over 7000 rare diseases. Roughly only 200 have some type of manageable treatment [1].

Niemann-Pick disease refers to a fatal inherited metabolic disorder. It is classified in a subgroup of lysosomal storage disorders called sphingolipidoses. Disease involves dysfunctional metabolism of sphingolipids, accumulation of harmful quantities of lipids in the spleen, liver, lungs, bone marrow, and brain [2].

There are 3 types of Niemann-Pick disease, types A, B and C [3]. In 1914 Albert Niemann, a German pediatrician, described a young child with an enlarged liver and spleen, enlarged lymph glands, swelling and darkening of the skin of the face. The child had brain and nervous system impairment and died in less than six months, before the age of two. Albert Niemann published the first description of what is now known as Niemann-Pick disease, type A, in 1914. Ludwig Pick described the pathology of the disease in a series of papers in the 1930s. Niemann-Pick C is one of 50-60 Lysosomal Storage Disorders [4].

Both NPC1 and NPC2 genes encode cholesterol-binding protein, required for the transport of cholesterol. Over 260 mutations have been identified in NPC1 gene. Mutations include: small deletions, missense mutations and point mutations [5].

The children with Niemann Pick C only have a childhood to live a lifetime.

Prognosis

Type A: Most (approx. 89%) cases being fatal by 18 months. Rest 2/3 years.

Type B: Children may live a comparatively long time, but may require supplemental oxygen because of lung impairment.

Type C: The life expectancy varies, some die in childhood, less severely affected ones can live into adulthood [3,4].

Diagnosis

Niemann Pick Type can be determined by taking a small piece of skin (“skin biopsy”) growing the cells (“fibroblasts”) in the laboratory, and studying their ability to transport and store cholesterol. Unfortunately there is no quick available test that will give you the answer. The transport of cholesterol in the cells is studied by measuring conversion of the cholesterol from one form to another (“esterification”).

The storage of cholesterol is assessed by staining the cells with a chemical (“filipin”) that glows under ultraviolet light. This can show whether the cholesterol is being stored inappropriately in lysosomes, the recycling centers of the cell.

It is important that both the transport and storage tests be performed, since reliance on one or the other may lead to an incorrect diagnosis or missed diagnosis of a variant form of NPC [6].

- DNA tests
- Bone marrow aspiration
- Liver biopsy
- Slit-lamp eye exam

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Pathophysiology

Enlargement of lysosomes and affected cells. Creation of many small uniform-sized vacuoles, imparting a foamy appearance to the cytoplasm.

Mechanism of cholesterol trafficking:

-In normal cells, LDL-derived cholesterol enters cells via endocytosis by the LDL receptor

-digested within the late endosomes and lysosomes

-bind to NPC1 located in the membranes

-transported to the ER& Golgi apparatus for recycling within the cell

-ultimately to the plasma membrane (where the majority of cellular cholesterol resides)

Further study was carried out on skin fibroblast for demonstration of unesterified cholesterol accumulation in cultured cells by filipin staining method, which is the characteristic of NPD type C.

This involves dysfunction metabolism of sphingolipids and sphingomyelin in lysosomes that results in accumulation of these in lysosomes.

Prenatal testing

Few centers offer tests for prenatal diagnosis. Available for type C. Cells can be grown from samples taken at around 11 weeks of pregnancy and then observed.

Symptoms

The main symptoms of the Niemann Pick type C are: delayed motor development beginning before age 2, sudden loss of muscle strength, progressive liver failure starting in infancy,early lung involvement without neurological disease.

Side effects of Niemann Pick Type C disease

Side effects of Niemann-Pick type C disease. When brain cell function is blocked NP-C children loss coordination (Gelastic Cataplexy), stumble, fall (ataxia) and eventually need to be in wheelchairs, sleep in a hospital bed and utilize other adaptive equipment [7]. As the disease worsens other devastating symptoms develop including loss of the ability to speak (Aphasia), swallow (Dysphagia), laugh, remember (dementia), trouble moving eyes (vertical gaze palsy) [8], and often seizures occur. The health of children with NPC deteriorates until ultimately, the disease claims the child's life [9].

Treatment

Used statins to monitor liver function. Zavesca is an inhibitor of the enzyme glucosylceramide synthase, which ia a glucosyl transferase enzyme responsible for the first step in the syntheses of most glycosphingolipids [10-12].

Case report

Medical history

Anamnesa a girl at the age of 3, from a first normal pregnancy, born at 36-37 weeks of gestation with a weight of 2050 grams and a length of 43 cm, a smooth neonatal period. On the 7th month (May 2013), infection of the upper respiratory tract established splenoheropatomegaly (spleen 4 cm, liver at 2 cm), and was hospitalized at the university hospital in the city of Skopje. From the trials conducted, anemia, slightly elevated ACAT, TORCH (Toxoplasma rubella cytomegalovirus herpes), myelogram, ammonia, beta-glycosidase, acid sphingomyelinase and beta galactosidase- to normal (Kreatinin kinaza) KK-single-magnified (1288 U / L) after which it is normalized, rapidly increased chitotriosidase-454 mcU / ml (<100). Liver liver biopsy-a degeneratively altered liver with fibrosis, which is probably due to hypoplasia of bile ducts. The child is excluded thalassemia; the father is the carrier of a mutation for Hb Leporre. A fixed heterozygous legacy of the most common mutation of the disease on Gaucher-p.N409S. Additional trials are required.

Objective condition

General condition, afebrile (without temperature). Weight 16.5 kg (SDS-Standard Deviation Score=0.66), height 100 cm (SDS=0.73), volume of chapter 51 cm (SDS=1.18). Skin-pale pink, turgor and elasticity of the propane, PMT-moderately represented. Chapter=with proper configuration and saved mobility. Facial dysmorphism: a prominent forehead, depression of the base of the nose, hypertension, macroglossia. DS: DC 18/min, breathing-vesicular. SSC: CF cardiac frequency 118/min, clear tones, no listening to noises.

The abdomen was on the chest level, soft and elastic, painless liver at 4.5 cm below the ribs, and the spleen at 6 cm. The tracheal and urinary tract without peculiarities. Neurological status is normal.

Paraclinic examinations

PKK: WBC 8.9 × 10 / L, RBC: 5.06 × 10 / L, HGB: 120 g / L, HCT: 35.7%, MCV: 70.6, MCH: 23.7 pg, MCHC: 336 g / L, PLT: 232 × 10^9 L, Lym: 44.9%, Gran: 45.2%, SUE: 16 mm

KCS-complete blood count

HCT-hematocrit volume of erythrocytes in a unit of full blood

MCV- average volume of erythrocytes

MCH-mean hemoglobin content in red cells

MCHC- mean hemoglobin concentration in erythrocytes

RDW - coefficient of variation in the distribution of erythrocyte volume

PLT- total platelet count

Biochemistry

AST - normal: 7-38 IJ / I

ACAT 83 U / L, alanine aminotransferase-ALAT 16 U / L enzymes of the hepar,

GGTP- Glutamyl Transpeptidase (GGTP) 10 U / L,

AF 239 U / L, KK (Creatinine kinase) 71 U / L, iron 12 μmol / l,

TIBC (Total iron binding capacity) 84.01 μmol / l.

Echocardiogram

The heart is normally anatomically and functionally. A marked common pulsed and reduced function of the left ventricle is observed. Unchanged valvular apparatus. No direct/indirect signs that would indicate myocardial valve damage at this stage.

Echogram of the abdominal organs

The liver-in DMKL (right lobe of the liver) 117 mm with a hyperhogeogenic structure, a rounded liver angle. Good circulation of pulmonary vessels: gall bladder without peculiarities; spleen enlarged 110 mm; kidney-without any specialty; the bladder is not sufficiently filled.

Radiography of the hand was also taken and showed disharmonic bone age, corresponding approximately to 3 years. 6 months-4 years.

Recommendations proposed by the doctors from Acibadem City Clinic Tokuda Hospital- Sofia, Bulgaria:

1. Make a consultation with a psychologist to be made

2. Test for the disease of Niemann-Pick type C

3. Control examination of clinical genetics after obtaining the results of the performed examinations

Request for: NPC1 (OMIM: 607623)-Niemann-Pick disease type C1 (OMIM: 257220), NPC2 (OMIM: 601015)-Niemann-Pick disease type C2 (OMIM: 607625), Niemann-Pick disease type A/B (OMIM: 257200)

Inheritance: autosomal recessive was send to Centogene AG, Rostock/Germany

Clinical information: dementia, mental retardation, splenomegaly, ataxia, hepatosplenomegalia, elevated chitotriosidosis

Result detail from the genetic center from Germany were: Lyso-SM-509 1, 7 ng/ml (reference: 0,8 ng/ml), NPC1 homozygous mutation c2819C>T (p.Ser940Leu), NPC2 no pathogenic mutation. The patient is suffering from Niemann-Pick disease type C1 due to a mutation in the NPC1 gene.

The concentration of the biomarker lyso-SM-509 was pathologically increased. The concentration of the biomarker lyso-SM-465, measured as an internal control was normal (18, 5 ng/ml, reference: <46, 3 ng/ml). These results are suggestive of Niemann-Pick disease type C, so we proceeded with the sequencing of the NPC1 and NPC2genes.

A homozygous mutation in exon 19 of the NPC1 gene, c. 2819C>T (p.Ser940Leu) was detected. This mutation has been previously described as disease-causing by Greer et al, 1999 (HGMD Professional 2015.4-PMID: 10521290)(13). The detected mutation is classified in class 1 according to CentoMD® and the ACMG recommendations (please, see additional information below for details on the classification).

Centogene variant classification (based on ACMG recommendations)

- Class 0-Likely pathogenic according to CentoMD®
- Class 1- Pathogenic
- Class 2- Likely pathogenic
- Class 3- Variant of Unknown Significance (VUS)
- Class 4- Likely benign
- Class 5 – Benign
- Class 6- Disease- associated variant
- Class 7- Likely benign according to CentoMD®

Methods used in genetic testing

The NPC1, NPC2 gene/s were analyzed by PCR and sequencing of the entire coding region and the highly conserved exon-intron splice junctions. The reference sequence(s) of the NPC1, NPC2 gene(s) is (are) NM_000271.4, NM_006432.3. The concentration of the biomarker lys0-SM-509 in dried blood spot was measured using high performance liquid chromatography (HPLC) HPLC and tandem mass spectrometry.

NPC1

- Location- Ex 19
- Nuc. Change- c2819C>T (homo)
- AA change - p.Ser940Leu
- RefERENCE - Greer et al [13]
- Evaluation- Disease causing

In the child MD, born 17.10.2012 year, from Kumanovo, on the basis of the clinical picture (anemia, organomegaly), biochemical, including genetic testing, the diagnosis of M.Niemann-Pick C. is diagnosed. It is a rare metabolic disease with an incidence of 1 × 120000. For the treatment of the disease in the European Union, Miglustat (Zavesca) as the only treatment. Caps. Miglustat (Zavesca) a 100 mg, 2 × 1 per day, a total of 732 capsules, or 9 packs of 84 capsules, total therapy for one year. A request for treatment of the girl has been submitted to the Committee for Rare Diseases, which exists within the Ministry of Health of the Republic of Macedonia, and has been approved.

Dental history

She was referred to the department for Pediatric and Preventive Dentistry within the University Dental Clinical Center Ss. Pantelejmon Skopje was sent by their own dentist due to the luxation of the two first central upper primaries incisive. Clinical dental examination found that the child presented dental development compatible with her age, acute gingivitis and dental caries on low second molars.

Discussion

The diagnosis of Niemann Pick Type C was complex due to low prevalence, a wide range of non-specific symptoms, oligosymptomatology (symptoms may be mild and in small numbers).Very often was misdiagnosed or unnoticed over many years. Also NP-C certification includes complex diagnostic testing, biochemical investigations (limited number of specialized centers), histological analyzes and genetic testing [14]. On the Internet it can find a program that helps doctors who come in contact with these patients to make the diagnosis easier [15]. Also dopamine transporter imaging (DaTSCAN) was used by Tomic S for diagnosis of the disease Niemann Pich type C [8]. In the literature several clinical case report are described [16,17].

Since she was first referred to the clinic, she has received preventative dental treatment every tree months. She and her parents have been instructed in oral health care, correct tooth brushing techniques and 0,12% chlorhexidine application to manage gingivitis. Manual prophilaxis was preformed and fluoride varnish was applied every 3 months. The importance of early diagnosis of the disease is essential for planning the future of the children, which helps families to access the support, advocacy, and appropriate early treatment, so as to prepare parents emotionally and physically strong for the future of their child, provides decision-making that allows them to spend better time with their child before the disease progresses and enables planning for the future. Also early diagnosis is important to better dental treatment and caries risk assessment of children with Niemann-Pick disease type C [11].The radiograph examination was not possible to be performed in this case. As the patient presented dysphagia, to prevent possible aspiration of deciduous teeth were extracted as soon as the parents noticed slight mobility of her teeth [21,22]. Since the patient was not cooperative for restoration of other teeth the general anesthesia was scheduled.

Future possible treatments for this rare disease can be enzyme replacement therapy and Gene therapy. Also there are attempts to treat this disease with stem cells [23-27].

Conclusion

Early diagnosis results in improved quality of life for the patient. The early adoption of preventive measures is important to reduce and control the risk of caries activity. Preventive measures, education, caregiver training, and frequent consultations with pediatric dentist are essential for patients with special health care needs.

Statement of conflict of interest

In the opinion of the authors, there is no conflict of interests

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