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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Monitoring of pregnancies with successful deliveries in a Niemann–Pick disease type B patient – case report and literature review

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SUMMARY

Introduction Niemann–Pick disease type B is an autosomal recessive disease caused by sphingomyelinase deficiency resulting in sphingomyelin accumulation in macrophages of various organs. Visceral involvement includes spleen enlargement, thrombocytopenia, dyslipidemia, sphingomyelin deposition in lung and liver, and bleeding risk. This is a rare disease and literature data about pregnancy in this setting are scarce. We present two favorable pregnancy outcomes in a patient with Niemann–Pick disease type B along with the review of the literature.

Case outline At the time of the first intended pregnancy, the patient was 34 years old. She had an extremely enlarged spleen, mild restrictive pulmonary disorder, hyperlipoproteinemia type IIb, thrombocytopenia with impaired aggregation tests. Cesarean section was indicated. She was prepared for delivery with platelet concentrates and prophylactic use of antibiotics. In the 36th week of gestation, a Cesarean section without complications was performed. The newborn's anthropometric parameters were BW 2490, BL 47 cm, HC 32 cm, and Apgar score was 7/8. The infant's development was normal. Three years later, in the second wanted pregnancy, the same examinations were done. The planned Cesarean section was done without complication after the same procedures, including prophylactic use of antibiotics and platelet concentrates, and a healthy female child was born.

Conclusion A multidisciplinary approach in female patients who suffer from lysosomal storage disease such as Niemann–Pick disease type B is essential and a favorable course is possible despite all risks.

Keywords: lysosomal storage diseases; platelet aggregation; splenomegaly; histiocytes

INTRODUCTION

Niemann–Pick disease type A and B are rare autosomal recessive diseases with an incidence of 0.4–0.6 per 100,000 newborns [1]. It is caused by sphingomyelinase deficiency resulting in sphingomyelin accumulation in macrophages of various organs. Niemann–Pick disease type C is a distinct disorder. Usually, in type B there are no neurological findings and patients survive in adulthood. Visceral involvement includes spleen enlargement, thrombocytopenia, dyslipidemia, sphingomyelin deposition in the lungs and the liver causing functional impairment and bleeding risk [1–5]. Pregnancy in this condition is always risky and a multidisciplinary approach is needed. Medline search revealed only three case reports of childbirth by women with this condition [6–8], and one with fatal postpartum hemorrhage [9].

CASE REPORT

We present two consecutive pregnancies in a 34-year-old woman with Niemann–Pick disease type B. Disease was suspected when she was 15 months old and splenectomy was suggested to her parents, but they refused it. A hematologist was consulted during the second hospitalization when the patient was 13 years old. She had abdominal pain after a minor trauma and an ultrasound examination revealed an enlarged spleen, which reached the pelvis and left lobe of the liver, without signs of injury. Bone marrow aspiration was performed and foam histiocytes and sea-blue histiocytes were seen. She started to visit a hematologist occasionally when she was a 23-year-old woman. A bone marrow biopsy was done and histology revealed hypocellularity, mild fibrosis, and groups of large cells with more stained cytoplasm, but there were no clear criteria for Niemann–Pick disease. Enzyme activities in cultured skin fibroblasts

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were determined at Universitätsklinik für Kinder und Jugendheilkunde in Graz, Austria. Clear deficiency of acid sphingomyelinase was detected and Niemann–Pick disease has thus been proven at the age of 23 years.

Before the intended pregnancy at the age of 34, marked splenomegaly, mild thrombocytopenia, and partial respiratory insufficiency were documented. According to her medical history, she had had two artificial abortions without recorded complication. She underwent inguinal hernioplasty at the age of 32, with postoperative bleeding that required platelet transfusion. Risk factors for pregnancy were presented to her: uterus pressure on the spleen and vice versa – spleen pressure on the uterus, potential for the worsening of respiratory symptoms, pressure on blood vessels, infection and hemorrhage, lower possibility that a child could carry the same disease according to recessive pattern of inheritance, and a realistic possibility for the fetus to have growth restrictions due to reduced space in the uterus. Hence, the patient decided to continue the pregnancy. Physical and laboratory findings were monitored monthly, and ultrasound examinations of the abdomen and portal vein system, lung capacity and echocardiography were done every three months. Results of complete blood count were stable, with mild anemia and platelet count 80–90 × 10^9/l. Repeated tests of hemostasis (fibrinogen, thrombin time, prothrombin time, activated partial thromboplastin time, fibrinolysis, D-dimer) were normal, while bleeding time was eight minutes (Ivy reference range being 2–7 minutes). Hyperlipoproteinemia type IIb with hypo-HDL cholesterolemia was present: cholesterol 5.8 mmol/l (2.6–5.2), triglyceride 2.38 mmol/l (0.1–1.7), HDL cholesterol 0.72 mmol/l, (1.6–3.88), Fried; LDL 4 mmol/l (2.07–3.4), non-HDL 5.08 mmol/l (0–3.86), LDL/HDL 5.55 (0–3), non-HDL/HDL 7.06 (0–3.25), cholesterol/HDL 8.06 (0–4.5). Platelet function test was performed prior to planned amniocentesis, revealing pathological findings, platelet aggregation was below lower limit: adenosine diphosphate 43 U (55–117), thrombin receptor-activating peptide 71 U (92–151), col. 30 U (61–108). Also, ultrasound examination of the abdomen and portal vein system was done: anteroposterior diameter of the liver was 17 cm, craniocaudal diameter of the spleen 22 cm, portal vein was not noticed. There were no signs of thrombosis in portal branches, flow speed was around 0.2 m/s. Platelet concentrates were reserved during the amniocentesis, but intervention was done without complication and there was no need for substitution. Normal male karyotype was found, but we had no possibility of genetic analyses for Niemann–Pick disease or enzyme activity measurement and the patient was given information that this result does not exclude the possibility that the child carries the same disease. We decided to prepare the patient for the planned Cesarean section with platelet concentrates. She was given corticosteroids for maturation of the fetal lungs. In the 35th + 5d gestational week Cesarean section was performed, with seven concentrates of platelets (1 per 10 kg of body weight) given before and seven during the procedure. She also received antibiotic prophylaxis. Newborn's anthropometric parameters were as follows: body mass 2490 g, body length 47 cm, head circumference 32 cm, and Apgar score was 7/8. There was no major blood loss and no need for red blood cell transfusion or transfusion of platelets in our patient's follow-up period. Three years later, she came to a hematologist in the sixth month of the second wanted pregnancy and the same examinations were performed. There was no sign of health deterioration in comparison with the previous pregnancy. A planned Cesarean section was done without complication after the same procedures, previously described, including prophylactic use of antibiotics and platelet concentrates before surgery, and a healthy female child was born. Infant development was normal in both cases.

The report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of the case report.

DISCUSSION

As aforementioned, Niemann–Pick disease is a rare disease and in clinical settings every health issue in these patients is challenging and searching for published data and learning from other's experience is mandatory. We decided not to do a splenectomy or partial resection of the spleen as spleen measurements did not differ significantly before and during the pregnancy, and there was no sign of spleen trauma. Also, we found the data about worsening of the lung function after this procedure in literature, caused by increased sphingomyelin accumulation in the pulmonary tissue [1–3, 10, 11]. We decided not to treat her for hyperlipoproteinemia because there is no proof about efficiency of that treatment in Niemann–Pick, and we tried to avoid potential elevation of liver enzymes [12]. Improvement in Niemann–Pick disease after injections of amniotic pooled placentas was described in literature and Porter et al. [6] mentioned improvement in liver function tests in their patient during pregnancy but without influence on hepatomegaly.

Searching on Medline we found only three reports of childbirth in women with Niemann–Pick disease type B. In the first one, published by Porter et al. [6], puerperal fever of unknown origin was observed, and according to the second one, Fried and Langer [7] used antibiotic prophylaxis. We decided to do the same due to our patient's splenomegaly and interstitial lung disease. In a case report published in 1997, the authors reported abnormal bleeding despite prophylactic treatment with vasopressin and need for blood and platelet substitutions [6, 7]. That data and findings of abnormal platelet function in our patient and experience with previous abdominal surgery led to our decision to give her platelet concentrates before the Cesarean section and according to the obstetrician's estimation during the operation. During the drafting of this work, we found a report of a fatal postpartum hemorrhage in a 23-year-old nulliparous woman with Niemann–Pick disease type B who concealed her disease from the obstetrician and her family [9]. In a study about cause of death in patients with Niemann–Pick disease type B, Cassiman et al. [13] reported that the main causes of deaths were respiratory and liver diseases, but hemorrhage was among the

leading causes and every patient who died of hemorrhage had splenomegaly and thrombocytopenia and half of them had liver disease or cirrhosis. Deaths associated with hemorrhage were reported after trauma, surgery, splenic vein tear, and gastrointestinal bleeding, and incidence was the same in patients who develop symptoms before and after the age of 18 years [13]. Due to a better diagnostic and supportive treatment and enzyme replacement therapy with olipudase alfa expected in the near future, other important issues come to horizon [14, 15, 16]. Prolonged survival and a better life quality are expected. Birth control in patients of reproductive age is another important issue and decisions about the type of contraceptives must be guided with their efficacy, metabolic effects and patient's adherence [17].

This case report emphasizes the importance of a multidisciplinary approach in female patients who suffer from lysosomal storage diseases such as Niemann–Pick type B and a favorable course is possible despite all risks [8]. Bleeding risk is not linked only to platelet count, but also to their function and the degree of splenomegaly. Liver impairment could exist and can influence hemostasis. Experience with previous pregnancies and invasive procedures in our patient along with the literature data influenced our treatment decisions. Pregnancies did not cause notable health deterioration in our patient and there are no clinical findings of Niemann–Pick disease or other significant health issue in children according to the pattern of inheritance of autosomal recessive diseases.

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NOTE

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Conflict of interest: None declared.

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Праћење трудноћа са успешним порођајима болеснице са Ниман–Пиковом болешћу тип Б – приказ болесника и преглед литературе

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САЖЕТАК

Увод Ниман–Пикова болест тип Б је проузрокована дефицитом сфингомијелиназе, што доводи до накупљања сфингомијелина у макрофагима различитих органа. Висцерални облик обично укључује присуство спленомегалије, тромбоцитопеније, поремећаја метаболизма липида, таложење сфингомијелина у јетри и плућима и повећан ризик од крварења.

Мултидисциплинаран приступ трудноћи код ових болесница је кључан. Ради се о реткој болести и подаци о трудноћи у овој ситуацији су изразито оскудни. Представљамо случај мултидисциплинарног праћења две трудноће са успешним порођајима болеснице са Ниман–Пиковом болешћу типа Б уз преглед литературе.

Приказ случаја У време прве жељене трудноће болесница је имала 34 године. Слезина је била изразито увећана, постојао је благ рестриктивни поремећај вентилације, хипер-липопротеинемија тип IIб, тромбоцитопенија с патолошким тестовима агрегабилности тромбоцита. Индикован је царски рез и болесница је припремљена концентратима тромбоцита уз профилактичку примену антибиотика. Оперисана је, без компликација, у 36. гестацијској недељи. Антропометријске мере новорођенчета су биле: ТМ 2490 *g* ТД 47 *cm*, ОГ 32 *cm*, Апгар скор је био 7/8. Три године касније у другој жељеној трудноћи урађени су исти прегледи и планирана секција без компликација, уз исте процедуре и припрему антибиотском профилаксом и концентратима тромбоцита.

Закључак Мултидисциплинаран приступ вођењу трудноће је неопходан код болесница са лизозомним болестима накупљања као што је Ниман–Пикова болест тип Б, а повољан исход је могућ упркос свим ризицима.

Кључне речи: лизозомне болести накупљања; агрегабилност тромбоцита; спленомегалија; хистиоцити