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TYPE I GAUCHER DISEASE (GDI) IN THREE SIBLINGS: ENZYME REPLACEMENT TREATMENT (ERT) REQUIRED

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Abstract: This is a family of three children, born to healthy Macedonian parents after uneventful pregnancies and delivery. The index child was an eight-year-old girl admitted for abdominal discomfort and distension: the spleen was 14cm below the costal margin (BCM), the liver 8cm BCM. No bone pain or pathology was reported. There was mild pancytopaenia (hemoglobin 11.2 gm/L; WBC counts 4.6×10^3; platelets 70×10^3). Liver function tests, renal ultrasound, bone scan, and a chest radiograph were within normal limits. Bone marrow analysis in this child and her two brothers (11 and 6.5 years old) revealed Gaucher cells. Both brothers had only mild anaemia, but the older brother had been splenectomized prior to diagnosis of GD1. Enzyme analysis revealed low activity (2.59, 1.62, and 2.55 nmol/h/mg protein, respectively); plasma chitotriosidase levels were also elevated. Genetic testing revealed homozygosity for the N370S/N370S mutation in all three siblings. In the absence of available enzyme replacement treatment (ERT), the girl was splenectomized. Removing an important immune organ (the spleen) introduces further risk for the patients. In addition, this does not solve the bone involvement characteristic for GD. ERT should be introduced for all GD1 patients in Macedonia.

Key words: Gaucher disease, N370S mutation, siblings, enzyme replacement therapy.

Introduction

Gaucher disease is the most prevalent lysosomal storage disease; the mode of inheritance is autosomal recessive. The disease results from an

inherited deficiency in the enzyme β-glucocerebrosidase. There are three clinical forms of Gaucher disease: Type 1 non-neuronopathic, Type 2 acute neuronopathic, and Type 3 subacute neuronopathic. Type 1 presentation reveals some ethnic-specific characteristics. The Type 1 form is most common among Caucasian patients, while the majority of Chinese patients have severe haematological and skeletal complications, and often neurological involvement, resulting in early childhood death. Herein, we report on three siblings with type 1 Gaucher disease.

Subjects and Methods

This is a family of three children (fig. 1), born to healthy Macedonian Albanian parents after uneventful pregnancies and delivery. Abdominal discomfort and bloating were the reason for the referral of the index child. This eight-year-old girl was found to have a spleen 14cm below the costal margin (BCM), while the liver was 8cm BCM. A blood cell count showed a mild pancytopenia (hemoglobin 11.2 gm/L; WBC counts 4.6×10^3; platelets 70×10^3). Liver function tests, renal ultrasound, bone scan, and the chest radiograph were within normal limits. Both brothers (11 and 6.5 years old) had only mild anaemia. Splenectomy was performed in Pristina in the older brother prior to the precise diagnosis of the reason for the splenomegaly. Bone marrow biopsy in all three children revealed Gaucher cells. No bone pain or pathology was reported in any of the children. The height of all siblings was within the normal range (25^{th}–50^{th} percentile) when corrected for mid-parental height. Enzyme analysis found that

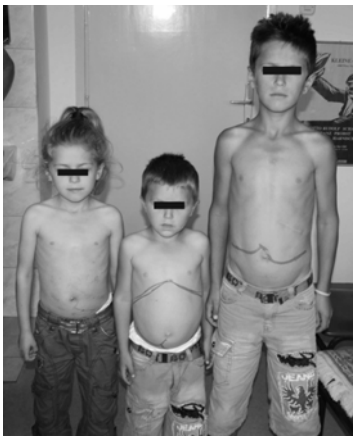

Figure 1 – Three siblings with Gaucher disease. Note the line of the hepatosplenomegaly, and the splenectomy scar
Слика1 – Двајца браќа и сестра со Гошеова болест. Забележете ја линијата на хепатоспленомегалија и лузните од спленектомија

leucocite β galactosidase was normal in all siblings and in the parents (143–211 nmol/h/mg protein; controls 70–400). Leucocyte β glucosidase was lower in the patients (2.59, 1.62 and 2.55 nmol/h/mg protein, normal in the parents (6.13 and

5.06 nmol/h/mg protein; controls 4.2–20). Plasma chitotriosidase (an important marker of the activity of the disease) was high in the patients (15.873, 9.755, 10.952 nmol/h/ml) and normal in the parents (30 and 11; controls 5–120). Genetic testing revealed homozygosity for the N370S (1226G) mutation in all three siblings. the parents' DNA was unavailable. Since ERT was unavailable, the parents decided to proceed with splenectomy in the daughter.

Discussion

Gaucher disease is clinically a very heterogeneous entity which usually presents in childhood with hepatosplenomegaly, pancytopenia, and manifestations of bone marrow infiltration by characteristic 'Gaucher cells'. Clinical severity ranges from affected infants to asymptomatic adolescents and adults. Characteristically there is no neurological involvement in type I GD.

Ocular pingueculae, or nodules, and dermal hyperpigmentation have also been described. GD was associated to monoclinal gammopathy or multiple myeloma [1], constrictive pericarditis [2, 3], clinical interstitial lung disease, white deposits in the corneal epithelium, anterior chamber angle, ciliary body, and pupil margin [4, 5], macular atrophy.

A large number (> 200) of different mutations of the GBA gene [6] have been described. Some genotype-phenotype correlations seem to exist. It is important to assess the precise degree of the severity of the disease as an indication for early enzyme replacement therapy.

The N370S found in our children is the predominant mutation in Mediterranean. Four mutations (N370S, L444P, R463C and D409H) comprise 75% of the investigated alleles in Greek patients. Interestingly, the N370S was only found in association with type 1 disease [7]. In Hungary, among non-Jewish GD patients, N370S, RecNciI, and L444P are the most prevalent mutations [8]. N370S is also the prevalent mutation in Romania [9]. In Ukraine, the N370S mutation was detected in 42.3% alleles, mutation L444P was observed in 15.4% alleles, and mutation 84GG was not found at all [10]. In Czech and Slovak patients, 78% of mutations were N370S, L444P, recNciI, and IVS2+1 [11]. Among 144 Italian patients, the most common mutations were N370S, L444P, RecNciI, G202R, IVS2+1, D409H, and F213I [12]. In 51 unrelated Spanish patients the two most common mutations were N370S and L444P [13]. Recombinations in the glucocerebrosidase gene locus were common among African-Americans, resulting in a significant genotypic heterogeneity [14].

ERT is a mainstream therapy today. Splenectomy, once the main treatment in GD, has shown that it is often followed by an increase in osteolytic lesions [15]. Therefore, some authors recommended partial splenectomy (minimizing the effect on bone and avoiding postsplenectomy sepsis). Obviously, in our children splenectomy was not our treatment of choice. The lack of ERT dictated the surgeon's decision.

Allogenic bone marrow transplantation was previously used in GD patients [16], but is no longer a treatment option. Gene treatment started early *in vitro* [17], but for the patients it is still a treatment of the future.

The enzyme (Ceredase) derived from human placental tissues was approved by the Food and Drug Administration in 1991, while the recombinant enzyme was approved by the FDA in mid-1994 [18]. A solid base of clinical experience with ERT has been gathered. In 1,028 Gaucher patients treated with ERT for 2 to 5 years an improvement in anaemia, thrombocytopenia, organomegaly, bone pain and bone crises has been well documented [19].

Some lysosomal storage diseases are caused by lysosomal enzyme variants. Those variants retain catalytic activity but are predisposed to misfolding and/or mistrafficking in the cell [20]. Chemical chaperones have been used to correct those defects [21, 22].

In brief, this is a rare family with all three siblings affected with GD1. Splenectomy was an unfavorable treatment option dictated by the lack of ERT. Severe cases, especially in childhood, must be treated with ERT.

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Резиме

ГОШЕОВА БОЛЕСТ ТИП 1 (ГБ1) КАЈ ДВАЈЦА БРАЌА И СЕСТРА: ПОТРЕБНА Е ЕНЗИМСКА ЗАМЕСТИТЕЛНА ТЕРАПИЈА

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Се работи за три деца од семејство на млади и здрави родители, родени по уредна бременост и породување. Прво од децата пристапи осумгодишното девојче заради мачнина и дистендираност на стомакот. Зголемениот стомак родителите го забележале уште во раниот доенечки период. Нејзиниот постар брат бил спленектомиран, без претходно дијагностицирана болест. Слезината беше палпабилна 14 cm под ребрата, а црниот дроб 8 cm. Немаше податоци за болки во коските. Беше пронајдена блага анемија (Hb 112 g/L), лесно намалени бели крвни зрнца ($4{,}6 \times 10^9$) и ниски тромбоцити (70×10^9). Нејзините двајца браќа имале благо намалени црвени крвни зрнца и хемоглобин (11,9 и 12,3 g/L), како и нормални вредности на тромбоцитите (289 и 388×10^3). Анализите за хепаталната функција биле нормални, како и ехотомографијата на бубрезите, радиоизотопскиот скен на коските и графијата на белите дробови. Висок процент на типични Gaucher-ови клетки биле најдени во пунктатот од коскената срцевина. Стернална биопсија била направена исто така и кај нејзините двајца браќа (11 години и 6,5 години) и кај нив биле најдени исти Gaucher-ови клетки. Тогаш и кај девојчето била направена спленектомија.

β-гликозидазата во леукоцитите била нормална кај сите деца и кај нивните родители (143–211 nmol/h/mg протеини; контролни вредности 70–400 nmol/h/mg), β-гликозидазата во леукоцитите била пониска кај пациентите (2,59, 1,62 и 2,55 nmol/h/mg протеини), нормална кај родителите (6,13 и 5,06 nmol/h/mg протеини; контролни вредности 4,2–20 nmol/h/mg), додека плазматската хитотриозидаза била висока кај пациентите (15,873, 9,755, 10,952 nmol/h/ml), а нормална кај родителите (30 и 11; контролни вредности 5–120 nmol/h/ml). Генетската анализа покажа постоење на 1226G (N370S) мутацијата кај сите три деца. Отстранување на важен имун орган (слеска) води до дополнителни ризици за пациентите. Истовремено, спленектомијата не го решава проблемот со засегање на коските кај деца со ГБ1. Според тоа се наметнува потребата деца со ГБ1 да се лекуваат со ензимска заместителна терапија.

Клучни зборови: Gaucher-ова болест, N370S мутација, ензимска заместителна терапија.

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