TRANSITORY DIABETES MELLITUS IN CHILDREN DURING TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Stencel D, Derwich K, Kaczmarek – Kanold M

Department of Pediatric Hematology and Oncology, Karol Marcinkowski University of Medical Sciences, Poznań.

Received 7 September 1998; revision received 12 April 1999; accepted 26 May 1999.

Key words: ALL in children, transitory diabetes mellitus.

ABSTRACT

Intensification of treatment of acute lymphoblastic leukemia in children causes the increase of side effects, in this number diabetes mellitus. This disorder has a different character from „real" diabetes, very complicated etiology and most often - transitory duration. The diabetogenic activity is attributed first of all to corticosteroids and L-asparaginase. Early diagnosis and proper treatment (cessation of diabetogenic drugs, a diet and insulin therapy) make possible fast regression of clinical and biochemical abnormalities and, what is the most important, enables a continuation of chemotherapy. We present 3 cases of transitory diabetes mellitus in children with acute lymphoblastic leukemia.

INTRODUCTION

Intensification of treatment of acute lymphoblastic leukemia (ALL) in children caused, that 65 - 75% of patients have actually a real chance to be cured (Clavell et al., 1986; Matsuzaki et al., 1996; Radwańska et al., 1994; Silverman et al., 1997). Unfortunately, this progress is associated with increase of frequency of various side effects, including diabetes mellitus and other hyperglycemic disorders.

According to Pastore et al. glycaemia disorders may occur in nearly 50% of children with ALL at diagnosis, especially those over 10 years of age and with diabetes in their family history (Pastore et al., 1984). This is according to decreased glucose recycling in blast cells, leukemic infiltration in pancreas, failure of insulin synthesis and secretion and to physical and psychical stress (Pastore et al., 1984). Among antileukemic drugs diabetogenic activity is attributed to glycocorticosteroids and L-asparaginase, especially in combination cases (Clavell et al., 1986; Matsuzaki et al., 1996; Nagura et al., 1994; Pastore et al., 1984; Skomra and Przybylska, 1992; Tatoń, 1985). Hyperglycemia due to steroid administration is related to the increased gluconeogenesis and decreased tissue susceptibility to insuline and thus to tissue glucose consumption (Kaiser, 1991; Tatoń, 1985). Clinically, steroid induced hyperglicemia is characterized by normal or nearly normal insulin secretion, lack of susceptibility to ketosis, acidosis and glycosuria in hunger period and, lastly, to regression or significant alleviation after cessation of leukemia treatment (Tatoń, 1985). Data concerning the frequency of occurrence of drug - induced diabetes are divergent: they range from 0,2% among ALL patients (Skomra and Przybylska, 1992) to 6-8% in general population (Tatoń, 1985). L-asparaginase as L-asparagine degreding enzyme causes decrease of protein synthesis, in this number insulin (Pastore et al., 1984; Skomra and Przybylska, 1992; Tatoń, 1985). Additional importance has disturbance of insulin receptors (Pastore et al., 1984), abnormal response of islet α and β cells to stimulating impulses (Skomra and Przybylska, 1992) and toxic failure of the pancreas (Derwich et al., in print; Nagura et al., 1994; Niemeyer et al., 1991; Skomra and Przybylska, 1992; Tatoń, 1985) and other organs (Kurylak et al., 1997). Hyperglycaemic states after L-asparaginase application were observed in 1-14% (Skomra and Przybylska, 1992) even in 23% of ALL patients (Pastore et al., 1984).

We present three cases of transitory diabetes mellitus after simultaneous application of glycocorticoids and L-asparaginase in children treated for ALL.

CASE DESCRIPTION

In all presented patients acute lymphoblastic leukemia of common type was diagnosed. Chemotherapy according to ALL-BFM 90 protocol, modified by Polish Pediatric Leukemia/Lymphoma Treatment Group for low

risk group (Radwańska et al., 1996) was applied in every case. In Table 1 the relevant data are presented: time of diabetes appearance, clinical symptoms and laboratory findings. In all three cases we administered diabetic diet and insulin treatment (Insulinum Actrapid, Mixtard 30 HM and Humulin R) in doses based on current glucose serum concentration, for 27, 10 and 5 days respectively. Additionally, in the first case, during the treatment with glucocorticosteroids, increase of blood pressure occurred (RR - 140/100 mmHg) and temporary application of a hypotensive drug (nifedipine) was needed. Moreover, elevated levels of aminotransferase (AlAt - 116 IU/l, AspAt - 178 IU/l, GGTP - 389 IU/l) and bilirubin (3,0 mg%) were found. In the PCR HCV-RNA test, the presence of hepatitis C virus in the serum was detected. In the second patient coexisting fungoid stomatitis, leucopaenia (700 G/l), thrombocytopaenia (49 G/l), decrease of the fibrinogen serum level (70 mg%), and increase of cholesterol (447 mg) and triglycerides (469 mg%) levels were noted. The activity of amylase and lipase in the serum was normal. We applied intensive therapy using broad spectrum antibiotics (ceftriaxone, cefuroxime, cefotaxime, netilmicin, fluconazole), symptomatic drugs (granulocyte colony stimulating factor, ranitidine), infusion fluids and - as a prophylaxis - co-trimoxasole and colistin. Coexisting hyperbilirubinemia (5,99 mg%) and hypertransaminasemia (AlAt - 255 IU/l, AspAt - 47 IU/l) in the third patient were treated simptomatically (Hepa-Merz and infusion fluids). Next, after achieving improvement of the clinical state and normalization of glycaemia we continued chemotherapy with application of corticosteroids and L-asparaginase, replacing dexamethasone with prednisone in case 1 and giving four doses of L-asparaginase in case 2 In case 3 treatment was performed without any changes in the protocol.

At present all three children are alive in first hematological and clinical remission, during the maintenance therapy. Despite application of complete prednisone dose in reinductions (i.e. 40 mg/m^2 of body surface) repeated hyperglycaemia was not observed.

DISCUSSION

Modern treatment of ALL in children is more effective, but not devoid of undesirable effects, which become more significant with therapy hyperglycaemic state, most often connected with the administration of L-asparaginase and glucocorticosteroids (Clavell et al., 1986; Derwich et al.; Kaiser, 1991; Matsuzaki et al., 1996; Nagura et al., 1994; Pastore et al., 1984; Tatoń, 1985; Wang and Chu, 1993). In the second of our cases hyperglicaemia occured during dexamethasone application according to II protocol, however in one case - already in the initial phase, it appeared after 5 days of prednisone therapy. In none of our patients (independently of their family history and of diagnostic tests) diabetes was detected. This fact points at the effects of the drugs and excludes, as is known from literature, the hyperglycaemic effect of leukemia itself (Pastore et al., 1984). It seems that etiology of diabetes occuring in leukemia patients is very complicated and covers every factor mentioned above. Pastore's et al. investigations about lack of significant differences in glucose serum levels before and after L-asparaginase application, show the role of the accumulation of drug doses, not only direct toxicity (Pastore et al., 1984). These authors also suggest, that leukemic process itself plays a basic role in the disclosure of diabetes, and the effect of the drugs is only indirect (Pastore et al., 1984). We did not observe typical diabetic symptoms and signs. One of our patients presented neurological symptoms (confusion), and one had abdomen and legs pain with coexistence of sleepiness and mild increase of thirst. All of them had hyperglicaemia (152 - 447 mg%), glucosuria (1,5 - 8%) and ketonuria (+/++ - +/+++). Lack of gasometry abnormalities was found to be the same as in other reports (Pastore et al., 1984; Skomra and Przybylska, 1992; Tatoń, 1985). The emphasis is put on normal insulin level, despite the decrease of synthesis during leukemia, which distinguishes it from „real" diabetes (Pastore et al., 1984; Tatoń, 1985). In all our cases we applied a similar therapy, i.e. steroids and L-asparaginase cessation, diabetc diet and insulin (Actrapid, Mixtard, Humulin R) in doses based on current glucose serum levels. Insulin therapy lasted 27, 10 and 5 days respectively. In the first case, insulin administration for a longer period than necessitated by glucose levels („insulin cover") made possible finishing antileukemic therapy. Other authors underline the possibility of recuring to chemotherapy protocol after diabetes regression, too. It covers as well corticosteroid as L-asparaginase application, even in cases with coexsisting serious complications (Clavell et al., 1986; Pastore et al., 1984; Skomra and Przybylska, 1992;). It should be stressed, that establishing of diabetes is not described. The transitory

Patient	Sex and age	Time of ocurrence of diabetes	Clinical symptoms	Steroids administration	L-asparaginase administration	Glycaemia / glucosuria	Ketonuria / gasometry abnormalities
1. M.G.	M, 12,5 yr	8. day of II protocol, after I protocol and one high dose methotrexate.	Awareness disturbances (confusion).	Prednisone – 90 mg/d for 28 days in I protocol. Dexamethasone – 15 mg/d for 8 days.	15.000 U - 8 times in I protocol and 1 dose in II protocol.	430 mg% / 1,5%	+/+++ No gasometry abnormalities
2. E.K.	F, 7 yr	16. day of II protocol, after protocol I and M.	Diffuse abdominal and legs pain, increased sleepiness and thirst.	Prednisone – 50 mg/d for 28 days in I protocol. Dexamethasone – 8 mg/d for 16 days.	15.000 U - 8 times in I protocol and 3 doses in II protocol.	160-447 mg% / 1,5-8%	+/+++ No gasometry abnormalities
3. M.S.	M, 14,5 yr	11. day of I protocol.	No symptoms.	Prednisone – 100 mg/d for 11 days.	Still no application.	152-588 mg% / 2-4,5%	+/++ No gasometry abnormalities

Table 1. Characteristics of three cases of diabetes mellitus in children with acute lymphoblastic leukemia.

character of glucose intolerance makes possible to exclude disclosure of typical diabetes. In all our patients, abnormalities in laboratory tests concerning liver function were detected, and in the first case - positive HCV RNA - PCR test and increase of blood pressure were found. These changes may be connected with leukemia duration, but may also confirm, that diabetes is only one of many different symptoms of toxicity connected with modern antileukemic therapy.

CONCLUSIONS

Diabetes occuring during therapy of acute lymphoblastic leukemia has a complicated etiology and differs in character from typical diabetes.

The patients obtaining diabetogenic drugs, i.e. corticosteroids and L-asparaginase, especially in combination, should be subject to careful clinical observation and systematic laboratory tests aimed at diagnosis of diabetes.

Early diagnosis of diabetes and application of right treatment permits early clinical and biochemical normalization, thereby continuation of antileukemic therapy, even with diabetogenic drugs application.

Use of insulin in the therapy of diabetes connected with leukemia may make reduce the period of hyperglycaemia and make continuation of chemotherapy easier.

Diabetes in leukemic patients has a transitient character and its establishing has not been reported.

REFERENCES

Clavell L A, Gelber R D. Four - agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N. Eng. J. Med. (1986); 315: 657 – 663.

Derwich K, Stencel D, Warzywoda M. Uszkodzenie trzustki w przebiegu terapii L – asparaginazą u dzieci z ostrą białaczką limfoblastyczną. Praca w druku.

Kaiser H. Praktyczna kortyzonoterapia, PZWL, Warszawa (1991); 16 – 20.

Kurylak D, Kurylak A. Wybrane niebezpieczne powikłania chemioterapii przeciwnowotworowej u dzieci. Ped. Pol. (1997); 72: 453 – 457.

Matsuzaki A, Ishii E. Treatment of High - Risk Acute Lymphoblastic Leukemia in Children Using the AL851 and ALHR88 Protocols: A Report From the Kyushu - Yamaguchi Children's Cancer Study Group in Japan. Med. Pediatr. Oncol. (1996); 26: 10 – 19.

Nagura E, Kimura K. Nation-wide randomized comparative study of doxorubicin, vincristine and prednisolone combination therapy with and without L - asparaginase for adult acute lymphoblastic leukemia. Cancer Chemother. Pharmacol. (1994); 33: 359 – 365.

Niemeyer C M, Reiter A. Comparative results of two intensive treatment programs for childhood acute lymphoblastic leukemia: The Berlin - Frankfurt - Münster and Dana - Farber Cancer Institute protocols. Annals of Oncology (1991); 2: 745 – 749.

Pastore G, Saracco P. Glucose Metabolism in Children with Acute Lymphoblastic Leukemia Treated according to Two Different L-Asparaginase Schedules. Acta Haemat. (1984); 72: 384 – 387.

Radwańska U, Michalewska D, Kołecki P, Armata J, Balwierz W, Jaworska J, Chybicka A, Kowalczyk J, Ochocka M, Pawelec K, Milewska R, Jakimczyk D, Śladkowska G, Zelenay E. Wyniki leczenia najczęstszych postaci ostrej białaczki limfoblastycznej w świetle 6-letnich doświadczeń Polskiej Grupy Pediatrycznej ds. Leczenia Białaczek i Chłoniaków. Ped. Pol. (1994); 69: 703 – 710.

Radwańska U, Michalewska D, Kołecki P, Derwich K, Armata J, Depowska T, Ćwiklińska M, Jaworska J, Chybicka A, Kowalczyk J, Odój T, Matysiak M, Zelenay E, Pawelec K, Milewska R, Jackowska T, Jakimczyk D, Wieczorek M. Wstępna analiza wyników leczenia ostrej białaczki limfoblastycznej mniejszego ryzyka przy użyciu wysokich dawek metotreksatu z pominięciem napromieniania mózgowia. Ped. Pol. (1996); 9: 49 – 54.

Silverman L B, Weinstein H J. Treatment of childhood leukemia. Curr. Opin. Oncol. (1997); 9: 26 – 33.

Skomra S, Przybylska T. Przejściowa cukrzyca z kwasicą ketonową w przebiegu stosowania L - asparaginazy u dziecka z ostrą białaczką limfoblastyczną. Pol. Tyg. Lek. (1992); 47: 31 – 32.

Tatoń J. Kliniczne zespoły spowodowane niepożądanym działaniem leków hormonalnych. In: Kliniczna farmakologia niepożądanego działania leków., ed. Tatoń J, PZWL, Warszawa (1985); 181 – 226.

Tatoń J. Niektóre metaboliczne zespoły spowodowane niepożądanym działaniem leków. In: Kliniczna farma-kologia niepożądanego działania leków., ed. Tatoń J., PZWL, Warszawa (1985); 252 – 261.

Wang Y J, Chu H Y. Hyperglycemia induced by chemotherapeutic agents used in acute lymphoblastic leukemia: report of three cases. Chung. Hua. J. Hsueh. Tsa. Chin. Teipei. (1993); 51: 457 - 461.