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Allogeneic fetal stem cell transplantation to child with psychomotor retardation – A case report

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SUMMARY

Introduction The consequences of autologous and allogeneic stem cell transplantation (stem cells of hematopoiesis), applied in adults and children suffering from leukemia or some other malignant disease, are well-known and sufficiently recognizable in pediatric clinical practice regardless of the indication for the treatment. However, the efficacy of fetal stem cell transplantation is unrecognizable when the indications are psychomotor retardation and epilepsy.

Case Outline With the exception of neurological psychiatric problems, a boy aged 9.5 years was in good general health before transplantation with allogeneic fetal stem cells. The main aim of allogeneic fetal stem cell transplantation was treatment of psychomotor retardation and epilepsy. After 13 months of treatment, he was admitted to hospital in a very serious, life-threatening condition due to sepsis and severe pleuropneumonia. The humoral immunity in the boy was adequate, unlike cellular immunity. The immune imbalance in terms of predominance of T-suppressor lymphocytes contributes to delayed and late development of sepsis and severe pleuropneumonia. The boy still shows the same severity of psychomotor retardation, dyslalia, epilepsy, strabismus and amblyopia.

Conclusion Implementation of fetal stem cell therapy for unconfirmed indications abuses the therapeutic approach, harms patients, misleads parents, and brings financial harm to the healthcare system of any country, including Serbia.

Keywords: stem cells; transplantation; homologous; epilepsy; psychomotor disorders; costs

INTRODUCTION

The purpose of this appeal is to contribute to knowledge about the delayed consequences of the treatment with allogeneic fetal stem cell transplantation in children, and about the relevance of the indications for this therapy. The consequences of different types of stem cell transplantations applied in adults and children suffering from leukemia [1], some other malignant disease [1], ataxia telangiectasia [2], or spinal injury [3] are known, but consequences of the treatment with human embryonic stem cells do not include severe infections [2, 4].

To date, some basic groups of stem cells (totipotent, pluripotent, multipotent, oligopotent, unipotent, adult) are known [5]. Fetal stem cells are pluripotent, they are seven to 12 weeks old, there are two types of them (fetal proper, extraembryonic), and they have very high differentiation potential, thus they can differentiate into wide range of cell types within a certain germ layer (ectodermal, endodermal, mesodermal), which is considered to be an advantage. Modern therapy recognizes division of stem cells [6], and their relevant applicability, so that 1) embryonic stem cells are used for treatment of patients with age-related macular degeneration, 2) tissue stem cells are used for treatment of blood, skin, genetic blood diseases, heart attack, critical limb ischemia, damage of the cornea, and 3) induced pluripotent stem cells are used for treatment of several neurological disorders (Down's syndrome, Parkinson's disease). However, the efficacy of fetal stem cell transplantation is unrecognizable when the indications are psychomotor retardation and epilepsy, and consequences of this therapy in the context of severe infection are not known [3]. In addition, treatment by transplantation of plant stem cells is still considered homeopathic in some countries [7, 8], and for this reason it deserves to be considered from a different standpoint.

We found that the damage of allogenic fetal stem cell transplantation in a child suffering from psychomotor retardation and epilepsy is greater than the benefits. It is necessary to set clear and precise indications for fetal stem cells treatment for both healthcare professionals and parents, in order to prevent misuse of the cell therapy, until there are completed controlled clinical studies available.

CASE REPORT

A boy aged 9.5 years with body weight of 32 kg was hospitalized in a serious general condition due to staphylococcal sepsis and inva-

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Table 1. Difference of immunology parameters and blood count before and 13 months after fetal stem cell transplantation

Immunology parameters and blood count	Reference ranges	Before transplantation of fetal stem cells	13 months after transplantation of fetal stem cells and one month after sepsis
B-lymphocytes – CD19+	9 ± 6% 0.21 ± 0.08 × 10^9/l	14.4% 0.7853 × 10^9/l	13.26% 0.3912 × 10^9/l
T-lymphocytes – CD3+	60 ± 9% 1.34 ± 0.02 × 10^9/l	59.3% 3.2337 × 10^9/l	63.92% 1.8856 × 10^9/l
T-helpers – CD4+	39 ± 5% 0.86 ± 0.01 × 10^9/l	35.6% 1.9413 × 10^9/l	37.2% 0.7015 × 10^9/l
T-suppressors – CD8+	23 ± 4% 0.52 ± 0.01 × 10^9/l	23.7% 1.2924 × 10^9/l	31.7% 0.5979 × 10^9/l
NK – CD16+	12 ± 6% 0.39 ± 0.01 × 10^9/l	10.3% 0.5617 × 10^9/l	10.26% 0.3027 × 10^9/l
Helper-suppressor ratio CD4+/CD8+	2.4 ± 0.9	1.5	1.17
White blood cells	4.0–8.8 × 10^9/l	13.3 × 10^9/l	5.85 × 10^9/l
Lymphocytes	19-37% 1.2–3.0 × 10^9/l	41% 5.453 × 10^9/l	50% 2.95 × 10^9/l
Monocytes	0.0–9% 0.00–0.80 × 10^9/l	9% 0.49 × 10^9/l	10% 0.59 × 10^9/l
Red blood cells	3.8–5.3 × 10^{12}/l	4.03 × 10^{12}/l	3.688 × 10^{12}
Hemoglobin	110–170 g/l	133 g/l	125 g/l
Platelets	120–380 × 10^9/l	273 × 10^9/l	202 × 10^9/l

NK – natural killers
Reference ranges are for a boy 9.5 years old [13].

sive pneumococcal pleuropneumonia. The admission took place 13 months after fetal stem cell transplantation, performed routinely in the Center for Transplantation of Organs, Tissues and Cells in Ukraine, with two successive doses intravenously and subcutaneously, one day after the other [3]. The quantity of stem cells was defined as the total amount of 2.1 ml per dose, while there is no data in the discharge list regarding the exact number of given cells. On the official website of this institution it is stated that the quantity of stem cells is one for every 10,000–15,000 cells in bone marrow and one for every 100,000 cells in the bloodstream [9, 10]. Additional data are not known to the patient's parents. Both samples of cell suspension are certified with a series of tests in terms of absence of bacteria and viruses (HIV1, HBV, HCV, HGV, CMV, EBV, HHV6, HSV1,2, rubella, parvovirus B19) and intracellular infections (*Treponema pallidum*, *Toxoplasma gondii*, *Chlamydia trachomatis*, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum parvum*) [8, 9]. Immediately prior to fetal stem cell transplantation, normal cytology-representation in the blood was determined immunologically by flow cytometry, as shown in Table 1. There is no information that the patient received immunosuppressants or corticosteroids, either before or after the treatment. With the exception of neurological psychiatric problems, the child was in good general health before treatment with allogeneic fetal stem cells.

Thirteen months after the fetal stem cell transplantation and a month after healed staphylococcal sepsis and invasive pneumococcal pleuropneumonia, there were significant differences in the immune cytology representation in the blood, while the relationship between T-helper and T-suppressor lymphocytes (1.5 vs. 1.2 helper-suppressor ratio CD4+/CD8+) were significantly disrupted in favor of T-suppressor lymphocytes (23.7% vs. 31.7%). The representation of B-lymphocytes was unchanged. Due to our suspicions regarding development and genesis of hematological or immunological diseases in the patient, bone marrow aspiration and biopsy were performed during the sepsis, and showed cellularity of the fourth degree, with increased presence of megakaryocytes and overproduction of myeloid lineage. Immunoglobulin levels were normal, as well as C3 and C4 complement components, which means that humoral immunity in the boy was adequate, unlike cellular immunity.

DISCUSSION

To date it has been known that the predominance of T-suppressor lymphocytes contributes to delayed and late development of stem tumors, teratomas or teratocarcinomas [2], abnormal growth of the brain and the spinal canal [11], but not to weakening of immunity, which clinically presents as life-threatening sepsis and severe pleuropneumonia. The patient continues to show the same severity of psychomotor retardation, dyslalia, epilepsy, strabismus, amblyopia, and regularly uses valproic acid at a dose of 35 mg/kg/day, and optionally diazepam – which proves to be an unsuccessful and costly treatment with fetal stem cells. The transplantation was performed using fetal stem cells in the case of an indication such as psychomotor retardation, which has been unknown so far, and by using a number of cells undisclosed to the public, all of which should be criticized. Such innovative treatments also carry substantial risks with them and the potential not only for well-known malignant transformation of transplanted cells [2], but for severe infections, such as sepsis or severe pneumonia and pleuritis, as shown in this case report. It is likely that this delayed immune imbalance in terms of the up-regulation

of cellular immunity presents a risk of severe infections as adverse effects of treatment with fetal stem cells.

It should be noted that the representation of B-lymphocytes was unchanged, which coincides with data presented in literature [10]. In the patient, humoral immunity was preserved and balanced – that is, transplantation of fetal stem cells did not affect the number and activity of B-lymphocytes.

Modern recommendations concerning the techniques and methods of stem cell transplantation, regardless of their origin, are that the localization of the affected tissues defines the required number of transplanted cells [12]. In current literature there are no precise recommendations on the calculated number of fetal cells for transplantation for patients with epilepsy and psychomotor retardation, nor are there any recommendations according to the patients' age [5, 9, 12].

This paper will hopefully deliver a strong message, a criticism, and raise a question among professional public about the benefit–risk balance of allogeneic fetal stem cell transplantation in children with psychomotor retardation, epilepsy, a condition after intraventricular/periventricular hemorrhage, and hypoxic ischemic encephalopathy. At the same time, there is a requirement set before hematologists and neurologists to determine clear and precise indications for fetal stem cell transplantation in children, and to describe the limits for the therapy's possibilities. The therapy should not be an uncontrolled experiment with sick children, and controlled clinical studies approved by ethics committees need to be performed. Implementation of any type of stem cell therapy for unconfirmed indications is an abuse of the therapeutic approach, does harm to patients, misleads parents, and brings financial harm to the healthcare system of any country, including Serbia.

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Алогена трансплантација феталним матичним ћелијама код детета са психомоторном ретардацијом – приказ болесника

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КРАТАК САДРЖАЈ

Увод Последице аутологне и алогене трансплантације матичних ћелија (матичне ћелије хематопоезе), које се примењују код одраслих и деце оболеле од леукемије и неких других малигних болести, добро су познате и довољно препознатљиве у педијатријској клиничкој пракси без обзира на то шта је индикација за лечење. Али ефикасност трансплантације феталним матичним ћелијама је непрепознатљива када су индикације психомоторна ретардација и епилепсија.

Приказ болесника Са изузетком неуропсихијатријских проблема, дечак узраста девет и по година био је доброг здравственог стања пре трансплантације алогених феталних матичних ћелија. Главни циљ алогене трансплантације феталних матичних ћелија био је лечење психомоторне ретардације и епилепсије. После 13 месеци, он је примљен у болницу у веома тешком, животно угроженом стању због сепсе и тешке плеуропнеумоније. Хуморални имунитет код дечака био је адекватан за разлику од ћелијског имунитета. Имунолошки дисбаланс у смислу превласти Т-супресорских лимфоцита доприноси одложеном и касном развоју сепсе и тешке плеуропнеумоније. Дечак још увек показује исту тежину психомоторне ретардације, дислалије, епилепсије, страбизма и слабовидости.

Закључак Примена терапије матичним ћелијама фетуса за непотврђену индикацију значи злоупотребу терапијског приступа, штету за пацијента, заблуду за родитеље и финансијску штету у здравственом систему у било којој земљи, укључујући и Србију.

Кључне речи: матичне ћелије; трансплантација; хомологна; епилепсија; психомоторни поремећаји; трошкови

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