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Mental disorders induced by steroids in the course of treatment for acute lymphoblastic leukemia in adolescents

Zaburzenia psychiczne indukowane steroidami u adolescentów w przebiegu leczenia ostrej białaczki limfoblastycznej

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Summary

Glicokortykosteroids (GKS) are an important element in children's cancer treatment. However, they can lead to many adverse somatic and behavioral symptoms, including psychic disorders, also quality ones. Especially exposed are the patients with acute lymphoblastic leukemia (ALL) treated with high doses of Prednisone (PRED) and Dexamethasone (DEXA), as well as patients with Hodgkin Disease (HD) treated with multiple DEXA cycles. The two described cases of psychic disorders observed at adolescent boys treated for ALL are a study of steroids-induced disorders' image, as well as treatment attempts. Moreover, the study is the introduction to stating procedure standards for psychic disorders during children's cancer treatment in Polish conditions.

Key words: leukemia in children, steroids treatment, mental disorders

Streszczenie

Kortykosteroidy (GKS) stanowią ważny element w leczeniu wielu chorób nowotworowych wieku dziecięcego. Mogą prowadzić jednak do wystąpienia wielu niepożądanych objawów somatycznych i behawioralnych, w tym zaburzeń psychicznych, także jakościowych. Szczególnie narażeni są pacjenci z ostrą białaczką limfoblastyczną (ALL) otrzymujący w protokołach terapeutycznych wysokie dawki prednizonu (PRED) i deksametazonu (DEXA), jak i pacjenci z chorobą Hodgkina (HD) wielokrotnie otrzymujący cykle z DEXA. Opisane w pracy dwa przypadki zaburzeń psychicznych u nastoletnich chłopców w przebiegu leczenia ALL stanowią studium obrazu zaburzeń wyindukowanych GKS, jak i podejmowanych prób leczenia. Jednocześnie praca jest wstępem do opracowania standardów postępowania wobec zaburzeń psychicznych w przebiegu leczenia nowotworów u dzieci i młodzieży w warunkach polskich.

Słowa kluczowe: białaczki u dzieci, leczenie steroidami, zaburzenia psychiczne

INTRODUCTION

Corticoids as widely available and used drugs are becoming an important weapon in the fight against many diseases encountered in pediatric practice. They also play a key role in the treatment of acute lymphoblastic leukemia (ALL). The effectiveness of these drugs seems to be unquestionable, playing fundamental role in the long-term treatment of ALL. Long-term use of glicocorticoids (GCS) causes serious side effects

such as abnormal fat distribution, obesity, hypertension, diabetes, myopathy, osteopenia, hepatomegaly, or immunosuppression manifested as a tendency to infections. In addition to somatic changes corticosteroids may cause a number of mental disorders in the form of mood disorder. Among them we can highlight problems such as anxiety, agitation, insomnia, mania and depression, and even psychotic states with delusions and hallucinations (1, 2). Data from the literature

Prośba o
rozwińnięcie
skrótów

Streszczenie
jest za krótkie.
Brakuje również
odpowiedniej
struktury:
Introduction, Aim,
Material and
methods,
Results,
Conclusions
/ Wstęp,
Cel, Materiał
i metody,
Wyniki,
Wnioski

estimate the incidence of these disorders in the 5 to 75% of patients treated for various reasons with doses of corticosteroids (3). A series of studies conducted in adult patients suggests that acute psychiatric states correlate with the amount of the dose. Severe psychiatric symptoms occurred in 1.3% of patients receiving < 40 mg prednisolone daily (or equivalent of the dose), in 4.6% of patients treated with prednisolone dose from 41 to 80 mg, and in 18.4% of patients treated with doses exceeding 80 mg per day. There are also other relevant factors, including family predisposition (4). Further studies show an increased incidence of psychiatric disorders in patients treated with doses of 40 mg of prednisone a day (5). Pediatric studies have confirmed that the dose of 40 mg/m² of prednisone a day increased risk of psychotic disorders (6). Thus, the data coming from the publications and numerous studies describes pediatric patients with the diagnosis of ALL as a group of the highest risk of psychiatric disorders in connection with the intake of high doses of corticosteroids (7, 8). These disorders may occur at different times from the beginning of treatment with steroids. Lewis and Smith estimate 11.5 days as the average time from the start of treatment to the first symptoms of psychotic disorders, 39% of disorders occur in the first week, 62% within two weeks, 83% within 6 weeks (9). Mental disorders can also occur during dose reduction and withdrawal of the drug, most often manifesting as depression, anxiety, and fatigue (10) as well as mania and disorders of consciousness (11, 12).

The mechanism of function of corticosteroids triggering psychiatric conditions in patients is not fully known. The likely effects are impaired synthesis of monoamines (such as serotonin, dopamine, catecholamines) which is caused by exogenous corticosteroids, or disturbance in the economy neuropeptide transmitters. Corticosteroids increase the level of dopaminergic activity, and also reduce the central and peripheral serotonin secretion which may lead to psychotic states (13, 14). Another probable mechanism of steroids' function is hippocampal nerve damage, which in the process of additive synergism with used chemotherapeutic drugs and cytostatics can increase the psychiatric side effects of treatment of ALL (15). In patients with episodes of steroid-induced psychiatric disorders elevated levels of corticosteroid receptor mRNA were stated, which may also indicate a genetic determinants of these processes (16). Elevated levels of endogenous corticosteroids (neurotransmitter) of tetrahydrodeoxycorticosterone (THDOC) induces a reduction in the level of allopregnanolone and can be found in many models of acute depression (17).

AIM

Analysis of cases of mental disorders induced by taking steroids during treatment of acute lymphoblastic leukemia in children over 12 years of age.

MATERIAL AND METHODS

The subject of analysis was the course of transient episodes of mental disorders in two patients with ALL and evaluation of mental state at certain points in time during intensive care and during long-term follow-up after completion of maintenance therapy. The average age of patients at diagnosis was 14.9 years. Episodes of mental dysfunction occurred twice, in both treatment protocols, at the time of reduction of steroids.

Medical records of two patients treated for acute lymphoblastic leukemia in oncology and hematology ward for children at Pediatric Hospital in Lublin were analyzed. Criteria for selection of patients for analysis: identification of ALL, the age at diagnosis over 12 years, the occurrence of an episode of mental dysfunction during intensive treatment, temporal association of the episode with the intake of steroids, the ability to conduct follow-up. The patients were treated according to therapeutic protocols in force at the time of diagnosis (BFM 97 and ALL-IC 2002). These protocols treatment of acute lymphoblastic leukemia in children are composed of several stages, and during intensive treatment (induction of remission/Protocol I and the consolidation of remission/Protocol II) request similar doses of steroids. Patients receive in Protocol I prednisone (1-28 days 60 mg/m²/day and 3 x 3 days at a dose reduced), and in Protocol II dexamethasone (1-21 days 10 mg/m²/day and 3 x 3 days at a dose reduced). Between these protocols patients receive protocol M not containing steroids.

During the treatment, patients are supported by a planned psychological care. In the first month of treatment were assessed: intellectual functioning (WISC-R), emotional functioning ("How are you" Choynowski, Skrzypek), personality functioning (16PF Cattell) and the functioning of the family system (interview). In addition, the mental state of patients were analyzed on the basis of interview and psychiatric examination at certain points in time during the intensive care (T0 – at the beginning of treatment, E1 – during the first episode, E2 – during the second episode), and during long-term follow-up after the completion of maintenance therapy (T1 – after intensive treatment, T2 – 3 months after the end of treatment, T3 – 6 months after treatment).

RESULTS

The subject of analysis was the course of psychiatric episodes showing temporal association with the intake of corticosteroids and evaluation of the mental state at specific points in time in two patients with ALL. The detailed course of disorders and psychiatric symptoms were presented in the case and table 1 shows a comparison of the course of mental state changes.

Table 1. Comparison of episodes of mental disorders in patients with ALL, taking into account the course of steroid therapy.

Characteristics	Patient A	Patient B
Gender/Age (years)	M/14.9	M/15.2
Treatment protocol	BFM 97	ALL-IC 2002
Protocol I/Doses of GKS/ Number of days	100 mg PRED/28 days Dose reduction/9 days	115 mg PRED/28 days Dose reduction/9 days
Psychiatric symptoms in the first episode of mental disorders/ E_1	Isolation Worse contact Psychomotor slowdown Depression Anxiety and crying	Isolation Worse contact Low mood
Time of occurrence	29th day of steroid treatment	10th day of steroid treatment
Length of occurrence E_1	7 days	27 days
Psychiatric consultation	Doxepin 2 x 10 mg	No recommendations
Protocol II/Doses of GKS/Number of days	16 mg DEXA/21 days Dose reduction/9 days	20 mg DEXA/22 days Dose reduction/9 days
Psychiatric symptoms in the second episode of mental disorders/ E_2	Auditory hallucinations Psychomotor agitation Suicidal thoughts & tendencies Irritability, Anxiety, Restlessness	Auditory hallucinations Agitation Fear of death Vegetative symptoms
Time of occurrence	22nd day of steroid treatment	23rd day of steroid treatment
Length of occurrence E_2	7 days	9 days
Psychiatric consultation	Pernazine 3 x 25 mg	Olanzapine 2 x 5 mg

PRESENTATION CASES

Patient A

14.9 year-old boy, treated for ALL (according to BFM 97). In the course of treatment according to the protocol I received 100 mg of prednisone daily. Treated for 37 days (28 days of treatment with the maximum dose, 9 days of dose reduction). During dose reduction on 29th-37th days of treatment, the patient was observed with psychomotor retardation, impaired verbal contact, loss of interest in surroundings and people, depression, isolation, anxiety and crying. Boy poorly responsive to commands, was conscious, but he would not answer questions or answered casually, briefly. Psychiatric consultation was commissioned. The examination stated an image of mental disorder with mixed anxiety and depressive symptomatology associated with somatic condition and treatment as well as the adaptive response of the disease and hospital stay. Treatment with doxepin 2 x 10 mg a day was implemented, causing the stabilization of the patient after 7 days. The boy talked to his mother, he was busier and interested in the environment. Protocol M (not expected to treat with CS) was performed without any aggravations of the boy's mental state. In spite of psychiatric treatment the patient showed a slightly depressed mood. During protocol II the patient received dexamethasone at a dose of 16 mg for 30 days (21 days of the maximum dose, the next 9 days of reduction). During the 22th day of therapy (first day of reduction) the boy attempted suicide, disconnected drain from the drip, and then drank 250 ml of detergent, resisted to an attempt to intervene, he was excited, he expressed suicidal thoughts aloud.

In psychiatric re-examining the patient remained in significantly lowered mood, revealing suicidal thoughts and tendencies. After a few days to the image of disorders joined irritability, anxiety, restlessness, and auditory hallucination of an imperative type – “get out of here, run”. The boy became agitated, hostile to others, verbal contact was becoming difficult, brief. No abnormalities were observed in the patient's self- and allomental orientation. Given the presence of psychotic symptoms, pernazine treatment was implemented in gradually increasing doses up to 75 mg/day. After 7 days, stabilization of the patient was gradually achieved. The boy did not reveal anxiety, became calm in behavior, mood and propulsion were normalized. He did not confirm the presence of auditory hallucinations. He did not speak delusional content. He remained in logical verbal contact. There was no loss of consciousness. The patient denied suicidal thoughts and did not reveal suicidal tendencies. Loss of auditory hallucinations and agitation, disappearance of suicidal thoughts.

Patient B

15.2 year-old boy treated for acute lymphoblastic leukemia (ALL-IC 2002). During treatment according to the protocol I received prednisone at a dose of 115 mg. Treated with corticosteroids for 37 days (28 of full dose 115 mg prednisone, 9 days of dose reduction). 10 days after the start of therapy, after reaching the maximum dose, the boy has become very little active, secluded and in low mood. Symptoms remained at the same level from 10th to 37th day. Steroid therapy was continued. Psychiatric symptoms disappeared completely after complete reduction of the dose of prednisone without the need for psychop-

harmacological intervention. During the Protocol M (no corticosteroids) no mood, behavior or propulsion disorders were observed. In the course of Protocol II the patient received 20 mg of dexamethasone (22 days of full dose, 9 days of reduction). On the first day of dose reduction anxiety and fear were observed in the patient, and behavioral indications pointed to intense hallucinatory experience. During the psychiatric examination the boy confirmed the presence of auditory hallucinations of unpleasant for the patient content – “damning voice of God”, “Rosary”, he reported fear of death, agitation and strongly expressed vegetative symptoms of anxiety were observed. The boy asked for a priest to perform an exorcism. The patient was treated with 2 x 5 mg of olanzapine. Within a few days, an improvement of the patient’s mental state and alleviation of auditory hallucinations were stated. The patient remained in a good, logical verbal contact. There was no loss of consciousness. Previously experienced anxiety subsided, and the boy remained in balanced mood and propulsion. On the basis of the above symptoms the diagnosis of mental disorders of exogenous hallucinosis type was established.

Preliminary psychological examination (made in the initial period of hospitalization) allowed to describe intellectual, emotional, and personality functioning of patient. Patient A revealed an average level of general intellectual functioning, with a clear advantage in verbal ability. In the test of manifest anxiety (“How are you” Chojnowski, Skrzypek) he received high scores on the scale of lies indicating a tendency to hide his difficulties. Personality profile analysis (Cattell 16PF) described the patient as a person rather timid (H), very submissive (E), dissatisfied with himself and his situation (F), with a weak character (G), and a significant hypersensitivity (I). Patient B revealed below-average general intellectual functioning level, with a clear limitation in non-verbal abilities. In the test of manifest anxiety

(“How are you” Chojnowski, Skrzypek) similarly received high scores on the scale of the lies indicating a tendency to hide his difficulties. Personality profile analysis (Cattell 16PF) described the patient as a person rather bold (H), rather dominant submissive (E), pleased with himself and his situation (F), pursuing to the stated aim (G), with less ability of critical assessment (B).

Based on interviews with parents family-related aggravations in both patients were found. Fathers disclosed various types of mental dysfunction (father of patient A – suspicion of paraphilia, the father of patient B – psychopathic, violent trait). Both mothers of passive-dependent style of functioning.

Table 2 shows the characteristics of the patients’ mental state at selected time points (T1, T2 and T3). Patient A was under the observation for 60 months (until 20 years of age and passing into the adult care), and Patient B still remains under care. Patient A, at the end of treatment/T1 revealed slowdown, sadness, was withdrawn and reported memory decrease. In the treatment the patient received pernazine in a dose of 3 x 25 mg a day. Three months after the completion of treatment/T2 he was still sad, slowed down and reported memory problems. As a treatment he received alprazolam in a dose of 3 x 1 mg. 6 months after treatment, still slowed down and sad, he received treatment with fluoxetine in a dose of 2 x 10 mg. Patient B at the end of treatment/T₁ was in logical contact, but was non-critical, unleashed and in elevated mood. The treatment was maintained with olanzapine at a dose of 2 x 5 mg. 3 months after treatment/T2 unleashing and lack of criticism remained, also the patient did not follow the doctor’s recommendations (applied stimulants, did not follow the diet). The treatment was continued with olanzapine in the same dosage. Evaluation of the patient’s functioning six months after the treatment revealed no improvement in patient’s functioning in the capacity

czy wszędzie 1 przy T₁ powinna być w indeksie dolnym? taki zapis występuje jedynie w tym jednym przypadku. Jeśli tutaj cyfra w indeksie dolnym, czy ta sama zasada nie będzie dotyczyć T₂ i T₃?

Table 2. Characteristics of mental state of patients in selected moments in time.

Characteristics of mental state	Patient A	Patient B	Treatment
Beginning of treatment/T ₀	Tendency to hide difficulties Passivity Weak character	Tendency to hide difficulties Lack of insight Lack of criticism	A: None B: None
I episode of mental disorders/E1	Slowdown Isolation Denial of contact	Isolation Anxiety Low mood	A: doxepine 2 x 25 mg B: None
II episode of mental disorders/E2	Auditory hallucinations Psychomotor agitation Suicidal thoughts and tendencies	Auditory hallucinations Psychomotor agitation Anxiety Vegetative symptoms	A: pernazine 3 x 25 mg B: olanzapine 2 x 5 mg
End of treatment/T1	Slowdown Sadness Withdrawal Memory deterioration	Logical contact High mood Unleashed Non-critical	A: pernazine 3 x 25 mg B: olanzapine 2 x 5 mg
3 months after completion of treatment/T2	Sadness Slowdown Memory deterioration	Unleashing Not following doctors’ recommendations Lack of criticism	A: alprazolam 3 x 1 mg B: olanzapine 2 x 5 mg
6 months after completion of treatment/T3	Sadness Slowdown	Lack of criticism Stimulants (nicotine, alcohol)	A: Fluoksetyna 2 x 10mg B: olanzapina 1 x 5 mg Relegation to family therapy

dotychczas 0 nie było w indeksie dolnym - prosba o ujednoczenie zapisu

of a critical evaluation of their own behavior, dismissive attitude to medical recommendations and usage of stimulants (alcohol, cigarettes) remained. The dose of olanzapine was reduced to 1 x 5 mg and system therapy was suggested to the family. In spite of difficulties, the patients continued high school education within individual mode.

DISCUSSION

In children and adolescents with cancer who receive glucocorticoids in the course of treatment may occur mental disorders (18, 19). Reports available in the literature are mostly the descriptions of individual cases of mental disorders at different stages of receiving GKS in teenage children with acute lymphoblastic leukemia (13, 20-23), and Hodgkin's disease (24). Patients treated for ALL, due to receiving high doses of corticosteroids are particularly at risk of unwanted complications such as mental disorders. Descriptions of observed psychiatric symptoms are usually consistent and include such changes in mental functioning as slowdown, depressed mood, lack of interest in surroundings, anxiety, and various psychotic symptoms, especially auditory hallucinations. The moment of occurrence of symptoms is associated primarily with a reduction of corticosteroids' dose (1) or with the inclusion of a cyclical corticosteroid treatment, as in the HD treatment protocols (24, 25). The symptoms observed in patients are very disturbing for treating teams, require psychiatric consultation and medication. In this field, there is a large diagnostic and therapeutic variance. Described cases show how therapeutic concepts have evolved. The main difficulties were both excessive psychological interpretation and high subjectivity in the descriptions of the symptoms (disorders were treated

as inadaptive) as well as the difficulty of choosing the right drug and dose caused by the fear of interactions and side effects during treatment for the underlying disease. Overview of this types of dilemmas is provided by conference reports by Samardakiewicz and coworkers (26-28). Thus, clearly outlines the need for consistency of approach to the steroid-induced mental disorders. Such guidelines have been developed in recent years within the International Psychooncology Society (IPOS) (29) and can be found in Polish publications (30). An interesting attempt to treat steroid-dependent disorders is a proposal to include risperidone, even in the situation of having to continue taking steroids (22, 23). Work on the creation of such standard in Polish centers of pediatric oncology and hematology should be continued. This also applies to the development of the standard of care for the cured patients, who according to recent reports (31, 32) more often take mood stabilizers and anti-depressants compared to healthy peers.

CONCLUSIONS

1. Children and adolescents receiving high-dose steroids (PRED and/or DEXA) in the course of cancer treatment are at risk of developing mental disorders.
2. Episodes of mental disorders in adolescent boys with ALL occurred at the time of the reduction of steroids and had similar elements in the psychopathological image, but differed in the field of applied medication and course of the subsequent functioning of patients.
3. Diagnosis and treatment of psychiatric episodes in children with cancer requires the development of standards of procedure in conditions of Polish centers of pediatric oncology and hematology, also after the completion of treatment.

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