Screening of subclinical P300 event-related potentials changes in childhood acute lymphoblastic leukemia survivors

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Abstract. Modern treatment of childhood acute lymphoblastic leukemia (ALL) has resulted in a high cure rate; however, it can cause central nervous system toxicity. In the present study, a group of 136 ALL survivors were screened for changes in P300. Therapy was conducted according to a modified New York (NY) protocol (30 patients) and two subsequent revisions of a modified Berlin-Frankfurt-Münster (BFM) protocol (32 and 74 patients). The control group consisted of 58 patients. The survivors had significantly prolonged mean latency of P300 (331.31±28.71 vs. 298.14±38.76 msec, P<0.001) and reaction time (439.51±119.86 vs. 380.11±79.94 msec, P=0.002) compared with in the control group. Abnormalities in the endogenous evoked potentials were observed in 36 patients (26.5%). The mean latency time was significantly longer in the treatment groups compared with in the control group (NY: 329.13±28.07 msec, P=0.001; pBFM: 332.97±23.97 msec, P<0.001; BFM95: 331.47±31.05 msec, P<0.001). The reaction time was equally prolonged in both groups. In comparisons between the studied groups and the control group the most significant prolongation was recorded in the NY group (461.8±140.3 vs. 380.1±78.04 msec, P=0.039). Significantly higher frequency of prolonged reaction time in non-irradiated patients that received BFM95 was also revealed (21.62 vs. 15.85%, P=0.007). In addition, radiotherapy significantly reduced the P300 wave amplitude (mean values: 10.395±5.727 vs. 12.739±6.508 mV, P=0.027). In conclusion, endogenous P300 event-related potentials may be a useful tool in screening of subclinical cognitive changes in ALL survivors.

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Abbreviations: ALL, acute lymphoblastic leukemia; NY, New York; BFM, Berlin-Frankfurt-Münster; EEG, electroencephalography; IFCN, International Federation of Clinical Neurophysiology; NMDA, N-methyl-D-aspartate

Key words: acute lymphoblastic leukemia, survivors, neurotoxicity, screening, evoked potentials

Introduction

Modern therapies in childhood acute lymphoblastic leukemia (ALL) increased cure rate to more than 80% (1). There are many potential reasons for this contemporary breakthrough. It has been attributed to the introduction of new chemotherapeutic agents, enhanced supportive care and risk-adapted therapy (1,2). As survival rates have significantly increased, more emphasis has been paid on the long-term side effects of the ALL treatment. Both chemotherapy and radiotherapy cause damage to the central nervous system. It should be remembered that brain is protected by blood-brain barrier. To obtain propter drugs concentrations in the CNS high doses of drugs penetrating to it has to be given together with intrathecal chemotherapy. Both causes brain damage. It was also proved that radiotherapy is the main reason for tissue damage (3).

As shown repeatedly, ALL therapeutic protocols cause changes in the central nervous system. Undoubtedly, white matter disturbances induced by demyelination and vascular abnormalities play a role in cognitive impairment caused by radiotherapy (4). In turn, there is a significant gap in the knowledge of central nervous system-related chemotherapy toxicity. Direct destructive effects on cerebral endothelial cells, brain white matter, blood flow and glucose metabolism as well as modification of immunological mechanisms might be involved in the development of central nervous system damage (5-7). The above-described changes may contribute to the development of cognitive impairment in ALL survivors.

In the complex neurologic assessment evoked potentials (EP) take an important place. They are the response of brain cortex or other part of central nervous system to stimulation and appear in a close temporal relationship with the stimulus used for stimulation. Depending on the time of occurrence of the response to the stimulus (latency), EP is divided into exo- and endogenous. Endogenous potentials (also called cognitive potentials or cognitive event-induced potentials) are the result of changes in electrical voltage associated with information processing. They do not directly depend on the type of

stimulus, but on the processes of thinking. The P300 potential is defined as the positive highest wave deflection, recorded in the leads from the central-parietal region and appearing in 250-700 msec from the action of an acoustic or visual stimulus. The biggest advantages of these neurophysiological techniques include their high sensitivity, non-invasiveness and the possibility of multiple repetition at a relatively low cost. It can be compared to common biochemical markers in oncology like LDH (8).

The aim of our study was to assess the value of screening of subtle P300 event-related potentials changes in childhood ALL survivors as well as to compare the observed changes in irradiated and non-irradiated groups of patients.

Materials and methods

Study groups and treatment protocols. A group of consecutive 136 patients, 66 males (48.5%), aged 4.9 to 27.9 (average 13.5±5.3) years who have completed ALL therapy, were included in the study. The psychomotor development at the beginning of the treatment and follow-up of all included patients was compliant with calendar age and all patients carried out their school duty in an undisturbed manner or they worked and were fully independent after completing their education. Moreover, no symptoms of central nervous system focal injury were found in any patient in the studied and control groups during the clinical evaluation. No preliminary psychological or neurophysiological tests were performed before starting treatment. The study group was divided in 3 subgroups according to treatment protocols introduced gradually by Polish Leukemia/Lymphoma Study Group. Applied modifications of treatment protocols were previously published (9). ALL therapy was conducted according to modified New York (NY) (30 patients, 17 males, 56.7%) and subsequent revisions of modified Berlin-Frankfurt-Münster (BFM) (106 patients, 49 males, 46.2%) regimens. Patients treated with BFM protocols were divided into two further groups. 32 children (14 males, 43.8%, 18 females, 66,2%) were treated with previous modified BFM (pBFM) protocols (BFM 81, 83, 86 and 87) in which, as in the NY program, prophylactic and/or therapeutic central nervous system radiotherapy in addition to chemotherapy was used. In turn, 74 children (35 males, 47.3%, 39 females, 52,7%) were treated with the BFM95 protocol without radiotherapy. Two of these children also received a second-line chemotherapy due to recurrence of the disease. Central nervous system involvement was found in 7 children, including single patients treated with NY and BFM95 and 5 patients treated with pBFM. None of the analyzed patients underwent allogeneic hematopoietic stem cell transplantation.

Cumulative doses of vincristine in NY programs amounted 26 to 89 mg/m^2 (60.8 mg/m^2 on average) and 30 mg/m^2 in BFM programs. In two children with recurrent disease the cumulative dose of vincristine was 35 mg/m^2. The radiotherapy dose in pBFM group was 13-36.4 Gy (mean 18.4 Gy), while in the group treated with NY programs -18.2-24 Gy (mean 18.3 Gy).

The study group was a part of the total historical group of ALL patients composed of 559 children (all patients with ALL treated in studied period). It included 74 NY, 384 pBFM and 91 BFM95 patients.

The control group consisted of 58 patients, 34 males (58.6%), aged 6-17 years (mean 12.2±3.3 years), who were hospitalized after a single syncope episode (n=29) and healthy subjects (n=29) who volunteered for consultation and consented to the examination. All patients in the control group were completely asymptomatic in everyday functioning and in neurological examination.

Methodology of P300 event-related potentials analysis. The auditory evoked P300 potential was performed in accordance with the recommendations of the International Federation of Clinical Neurophysiology (IFCN) (10). In the study, a method of acoustic stimulation with two contrasting stimuli was used. Each time 60 responses to stimuli different from the background were averaged. Responses were recorded with surface cup electrodes located in the frontal (Fz), central (Cz) and parietal (Pz) zones. The reference electrodes were placed on the earlobes. Each patient underwent three procedures for averaging distinctive stimuli. The attention of the patients was controlled by pressing the counter at the moment of the appearance of the stimulus. To exclude the influence of body temperature on the conduction speed, the temperature was measured with a validated surface thermometer in each patient. To avoid the impact of emotional factors on the course of the study and the obtained results, all measurements were made in a quiet shaded room after a thorough explanation of the purpose and course of the study. In addition, none of the patients had been treated pharmacologically for at least 1 week prior to P300 potentials assessment.

According to the IFCN recommendations, the P300 potential was assumed as the positive wave with the highest amplitude recorded in the Pz lead, which appeared in the range of 280-500 msec. The latency, amplitude of the P300 wave and response time were evaluated in detail. Prolongation of the latency and the reaction time of the P300 wave above 2SD and a decrease in the amplitude below 1SD from the mean value were assumed as abnormal. To evaluate the effect of treatment, comparisons of ALL patients (NY, pBFM, BFM95) were made with the control group. In turn, to assess the impact of radiotherapy on the obtained P300 parameters, the NY + pBFM group was isolated and compared with the non-irradiated group (BFM95).

The study protocol complied with the Declaration of Helsinki and was approved by the Jagiellonian University Medical College Ethics Committee (Consent No. KBET/131/B/207). All parents and patients above 16 years old signed written informed consent before inclusion in the study.

Statistical analysis. Statistical analyses were performed with Statistica 12.0 (StatSoft, Statistica 12.0, Tulsa, Oklahoma, USA) software. Continuous variables are expressed as mean ± standard deviation and categorical variables as number (percentage). Continuous variables were first checked for normal distribution by the Shapiro-Wilk statistic. Differences among two groups were compared by unpaired Student's t-test when normally distributed or by the Mann-Whitney test with test for non-normally distributed variables. In turn, differences among multiple groups were compared by one-way ANOVA test followed by Scheffe test when normally distributed or by the Kruskal-Wallis test followed by Dunn's post-hoc test for multiple comparisons for non-normally distributed variables.

Table I. Comparison of P300 potential parameters among the individual protocols and the control group.

Characteristic	NY (n=30)	pBFM (n=32)	BFM95 (n=74)	Control group (n=58)	P-value
Starting treatment, years	6.5±4.5	4.4±3.1	4.9±2.5	-	0.120
Mean age, years	14.0±5.6	18.3±4.0	11.2±4.0	12.2±3.3	<0.001[a]
Total sum of abnormalities	10 (33.33%)	5 (15.63%)	21 (28.38%)	-	0.247
Prolonged P300 latency	1 (3.33%)	0	4 (5.41%)	-	0.522
Decreased P300 amplitude	0	0	0	-	-
Prolonged reaction time	10 (33.33%)	3 (15.63%)	16 (21.62%)	-	0.007[b]
P300 latency, msec	329.13±28.07	332.97±23.97	331.47±31.05	298.14±41.57	<0.001[c]
P300 amplitude, mV	9.29±4.81	11.43±6.37	12.74±6.51	9.64±7.29	0.036
P300 reaction time, msec	461.8±140.3	395.1±99.08	449.7±115.77	380.1±78.04	0.006[d]

BFM, Berlin-Frankfurt-Münster; NY, New York. [a]P=0.039 NY vs. control group, P<0.001 pBFM vs. control group, P=0.026 BFM95 vs. control group, P=0.001 NY vs. pBFM, P=0.010 NY vs. BFM95, P<0.001 pBFM vs. BFM95; [b]P<0.001 NY vs. pBFM, P=0.021 NY vs. BFM95; [c]P=0.001 control group vs. NY, P<0.001 vs. pBFM, P<0.001 vs. BFM95; [d]P=0.039.

Table II. Comparison of P300 potential parameters in irradiated and non-irradiated groups of patients.

Characteristic	NY + pBFM (n=62)	BFM95 (n=74)	P-value
Starting treatment, years	5.3±3.7	4.9±2.5	0.690
Mean age, years	16.3±5.2	11.2±4.0	<0.001
Total sum of abnormalities	15 (24.19%)	21 (28.38%)	0.581
Prolonged P300 latency	1 (10.0%)	4 (5.41%)	0.522
Decreased P300 amplitude	0	0	-
Prolonged reaction time	13 (15.85%)	16 (21.62%)	0.007
P300 latency, msec	331.113±25.891	331.473±31.048	0.941
P300 amplitude, mV	10.395±5.727	12.739±6.508	0.027
P300 reaction time, msec	427.371±124.423	449.689±115.772	0.284

BFM, Berlin-Frankfurt-Münster; NY, New York.

Categorical variables were analyzed by the χ^2 test and Fisher's exact test depending on the size of the analyzed groups. P<0.05 was considered statistically significant. Due to similar age and gender distribution in the patient and control groups, no additional statistical analysis of those parameters was performed.

Results

Analysis of study groups. Mean age of children at the time of starting treatment was 5.1±3.2 years. In turn, mean age at the time of screening for cognitive disorders was 13.5±5.3 years. The time that elapsed from the completion of treatment to performed screening ranged from 1.5 to 21.8 years.

Mean age of starting treatment in NY group was 6.5±4.5 years and mean control age -14.0±5.6 (Table I). Children treated with pBFM developed ALL at younger age (4.4±3.1 years) and were controlled at older age (18.3±4.0 years). In this group, the average time from onset of the disease to control was therefore the longest. In turn, the difference between the average age of ALL onset (4.9±2.5 years) and the average age of control (11.2±4.0 years) was the shortest in the BFM95 group. However, the statistical analysis did not show any significant differences in the mean age of ALL onset. In turn, the mean age of cognitive control was significantly different (P<0.001). Intergroup differences were shown between particular treatment regimens as well as in their direct comparisons with the control group (Table I).

In groups with or without radiotherapy, the average age of starting treatment was similar, while patients with radiotherapy were significantly older at the time of control examination (mean age: 16.3±5.2 vs. 11.2±4.0 years, P<0.001) (Table II).

The psychomotor development was compliant with calendar age and all patients carried out their school duty in an undisturbed manner. Moreover, no symptoms of central nervous system focal injury were found in any patient during the clinical evaluation.

Analysis of P300 evoked potentials in individual protocols. The total group of ALL survivors had a significantly prolonged mean P300 latency (331.31±28.71

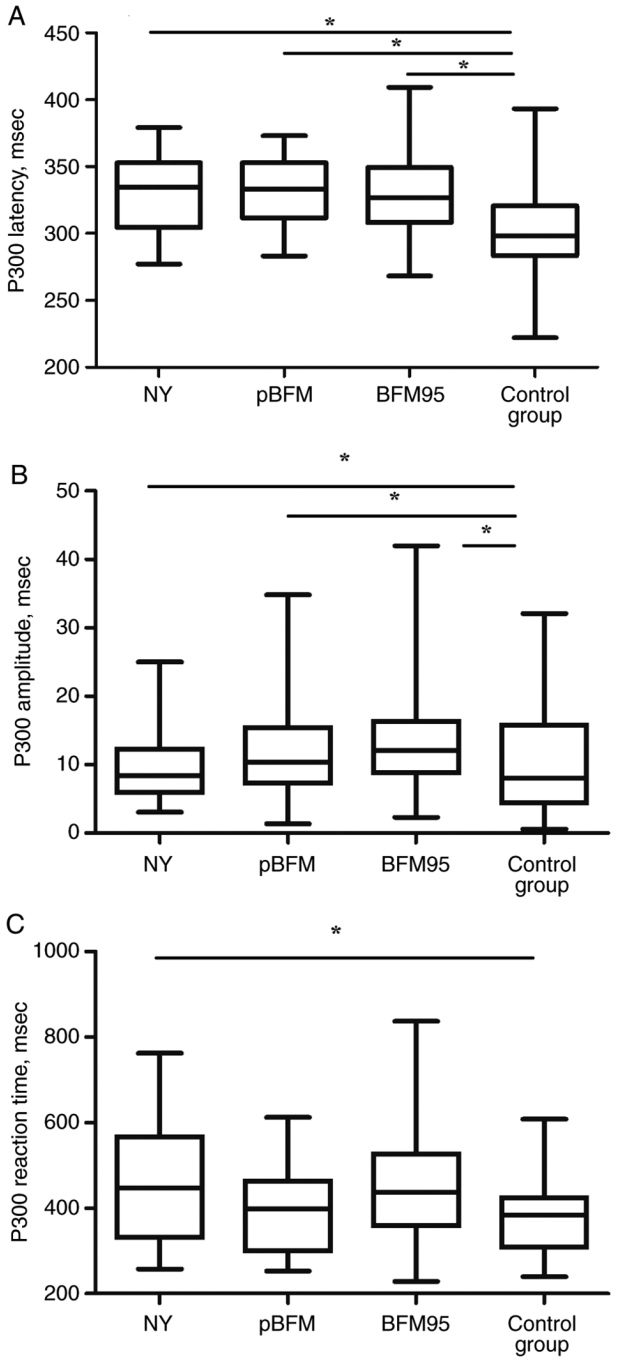

Figure 1. Differences in P300 potential parameters between study groups. (A) P300 latency. (B) P300 amplitude. (C) P300 reaction time. *P<0.05. BFM, Berlin-Frankfurt-Münster; NY, New York.

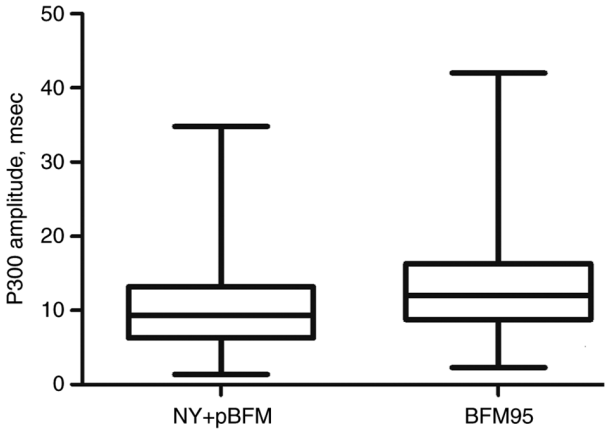

Figure 2. Negative impact of radiotherapy in NY and pBFM protocols on P300 wave amplitude. BFM, Berlin-Frankfurt-Münster; NY, New York.

vs. 298.14±38.76 msec, P<0.001) and reaction time (439.51±119.86 vs. 380.11±79.94 msec, P=0.002) compared to the control group. No differences were observed in the average amplitude of the P300 potentials (11.67±6.25 vs. 9.64±7.32 mV, P=0.179).

Mean P300 latencies in NY, pBFM and BFM95 were 329.13±28.07, 332.97±23.97 and 331.47±31.05, respectively. The average amplitude of the P300 potentials and P300 reaction time in studied groups were 9.29±4.8, 11.43±6.37, 12.74±6.51 and 461.8±140.3, 395.1±99.08, 449.7±115.77 respectively (Table I). No statistically significant differences in comparison of analyzed parameters between groups with ALL were noticed. The differences in P300 potentials parameters between study groups were presented in Fig. 1.

Significant changes were found in the screening with endogenous evoked potentials in 10 (33.33%) NY patients. In turn, the results of this study were abnormal in 5 (15.63%) pBFM and 21 (28.38%) BFM95 patients. There was no significant difference in the total frequency of their occurrence in individual treatment groups (Table I). In the NY group, prolonged P300 latency was found in 1 patient and a prolonged reaction time in 10 patients. The incidence of prolonged reaction time was significantly higher than in other groups (P=0.007). In the pBFM group, P300 latency was normal in all patients, while in the BFM95 group latency was abnormal in 4 patients. In contrast, the prolonged reaction time was recorded in 3 pBFM and 16 BFM95 patients. There was no reduction in P300 amplitude in any patient.

Significant differences between the individual protocols were observed in all measured parameters characterizing the P300 evoked potentials (Table I). The mean latency time was significantly longer compared to the control group (298.14±41.57 msec) in all analyzed protocols (Fig. 1A). The highest values were observed in pBFM patients (NY: 329.13±28.07 msec, P=0.001; pBFM: 332.97±23.97 msec, P<0.001; BFM95: 331.47±31.05 msec, P<0.001) (Fig. 1A). At the same time, however, no intergroup differences were found between the protocols analyzed in this study.

The combined analysis of the P300 wave amplitude in individual groups using the Kruskal-Wallis test signaled a significant difference (P=0.036) (Fig. 1B). However, further analysis of the average amplitude values in the pair-comparison test did not reveal differences between individual groups.

The reaction time was similarly prolonged compared to the control group. Its largest and significant prolongation was noted in the group treated with NY (461.8±140.3 vs. 380.1±78.04 msec, P=0.039) (Fig. 1C).

Impact of radiotherapy on P300 potential parameters. Abnormalities in the screening with endogenous evoked potentials were observed in 15 (24.19%) patients treated with NY + pBFM protocols. Analyzing the frequency of individual P300 potential abnormalities, a significantly higher frequency of reaction time prolongation was found in non-radiated patients

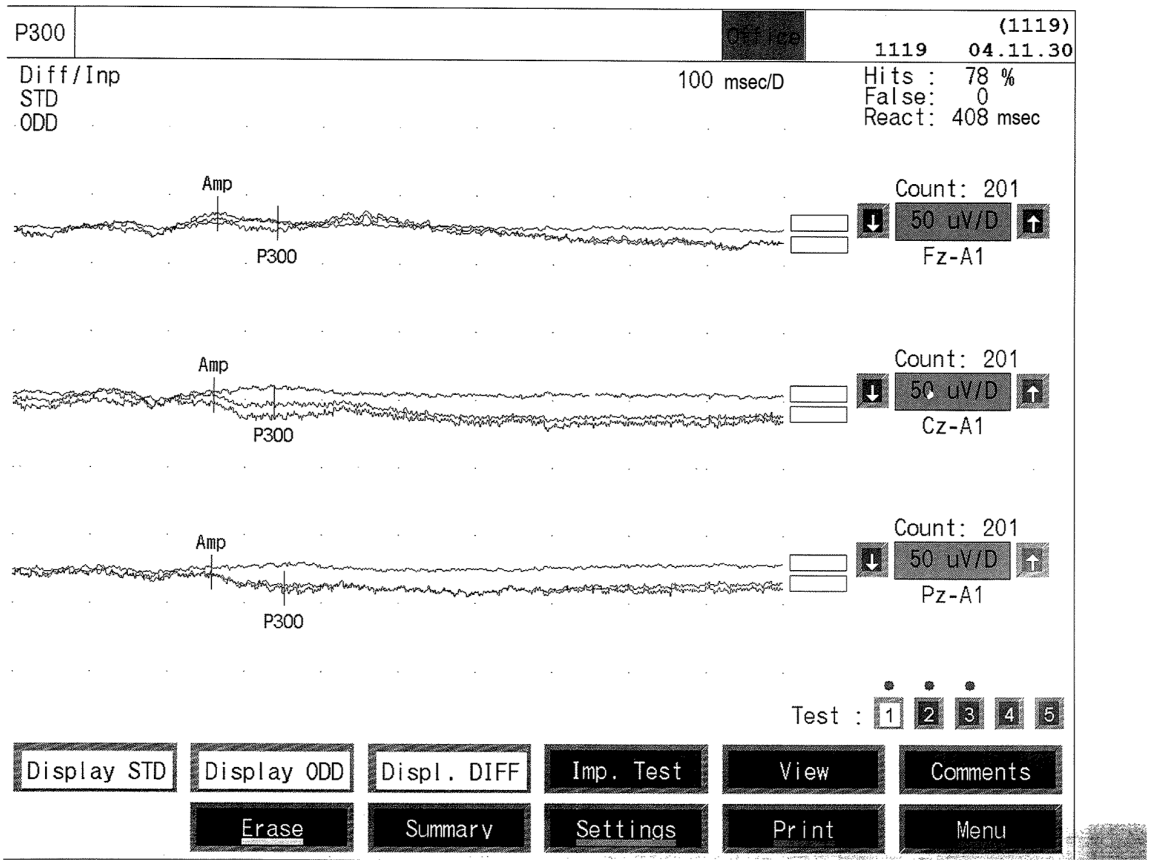

Figure 3. P300 wave in a patient treated with New York protocol.

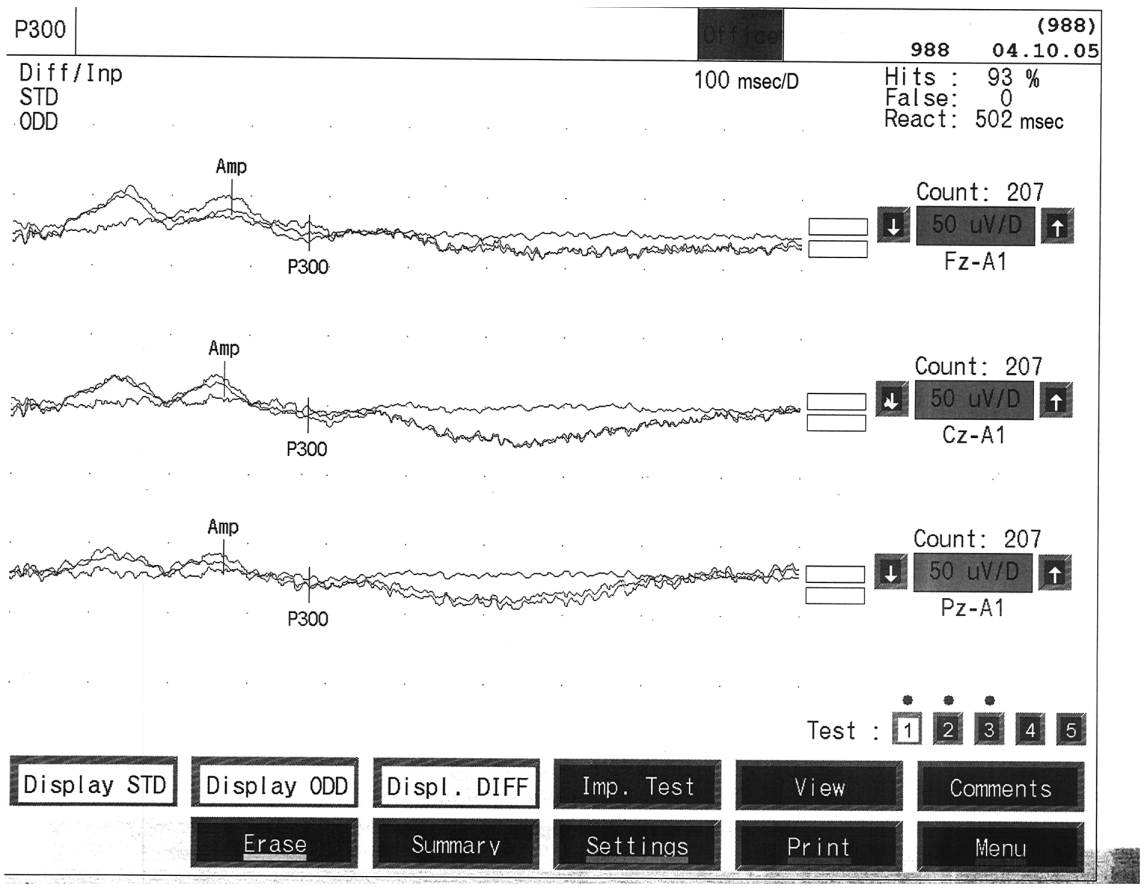

Figure 4. P300 wave in a patient treated with BFM-95 protocol.

treated with BFM95 (21.62 vs. 15.85%, P=0.007). Despite the lack of a decrease in P300 amplitude meeting adopted criteria in both analyzed groups, a statistical analysis showed a significant lowering impact of radiotherapy on the P300 wave amplitude (mean values: 10.395±5.727 vs. 12.739±6.508 mV, P=0.027) (Fig. 2). No significant differences were observed in the other analyzed parameters. The examples of P300 wave in patients treated with NY and BFM95 protocols were shown in Figs. 3 and 4.

Discussion

P300 are an objective but non-target diagnostic tool. The analysis of the results included the assessment of the morphology, the record of the latency and amplitude of the obtained potentials. Latency elongation above 2-2.5 SD, amplitude changes above 50%, as well as incorrect morphology were considered abnormal. The parameters of evoked potentials change with the maturation of the nervous system and it is assumed that P300 latencies reach values similar to those in adults at the end of the first decade of life (10). In turn, the results of somatosensory evoked potentials latency are the result of two processes: on the one hand, the growth of the child and the elongation of limbs (and thus the extension of latency), and on the other hand, the maturation of the nervous system (shortening latency). Currently, it is assumed that the values of P300 parameters are similar to those of adults at the end of the first decade of life (10).

Stimulation with two distinctive acoustic stimuli (oddball paradigm) is commonly used, and the P300 wave is formed after 300-800 msec from the action of the stimulating stimulus. It is generally accepted that its latency is a measure of the time needed for the course of cognitive processes preceding the cognitive assessment of the task situation, while the size of the amplitude of this fraction is a measure of the involvement of cognitive structures (10). In turn, the correct reaction time indicates a good focus of attention. This breakdown occurs when the recognition of a stimulus is associated with a high level of subjective uncertainty and is a measure of the degree of attention paid to a specific cognitive task. The P300 wave arises at the end of a specific cognitive process and has the highest amplitude in the leads from the parietal region. It is assumed that it is generated in the hippocampus area and in the temporal and parietal lobes of the cerebral cortex (11). The P300 was first used in the diagnosis and monitoring of dementia syndromes. Successively in the diagnosis of demyelinating diseases, metabolic diseases, CNS tumors, phakomathoses, neuroinfections and post-traumatic lesions. Of particular interest is the application of endogenous potentials in patients with attention deficits with hyperactivity and specific learning difficulties (12).

Several meta-analyses concerning neuropsychological outcomes after treatment for childhood ALL have been developed so far. All of them unanimously emphasize the heterogeneity of the studied populations and the lack of a uniform cognitive impairment analysis scheme in ALL patients. In the literature review of neuropsychological consequences of ALL chemotherapy approximately two thirds of analyzed studies found declines in different aspects of cognitive functioning (13). Cousens *et al* (14) analyzed 31 studies reporting cognitive function in ALL children after cranial irradiation. Decrements were found in intellectual function, amounting to 10 intelligence quotient points. Campbell *et al* (15) performed a complex meta-analysis of 28 studies, those with cranial irradiation, as well as studies in which treatment solely consisted of chemotherapy. As has been shown, ALL survivors show significant deficits in intellectual and neurocognitive functioning which resulted in worse academic achievements. Moreover, ALL patients treated with cranial irradiation performed worse intellectually than those who received only intrathecal chemotherapy. In turn, Peterson *et al* (16) analyzed neuropsychological results of ALL treatment with chemotherapy only. Based on 13 articles published until 2004, some evidence for mild fine motor, executive function and verbal memory weaknesses existed in these patients. In addition, the direct relationship between higher levels of methotrexate and executive dysfunction has been recently reported (17). This was also confirmed by the diverse activity of particular brain regions visualized with structural and functional magnetic resonance imaging (15).

Currently, the American Academy of Pediatrics indicates neuropsychological follow-up as an important element of long-term care for cancer survivors (18). However, this recommended approach is not without drawbacks. There is still insufficient evidence to guide the specific timing of comprehensive neuropsychological assessment for children with ALL. Moreover, neuropsychometric evaluation can be expensive, time-consuming and provide limited insight into the neurobiological basis of cognitive dysfunction. As a consequence, there is a need for simple functional methods to screen which patients need extensive neuropsychological testing and possible rehabilitation to optimize their learning capabilities and academic achievements. Conventional EEG (electroencephalography) recordings have not turned out to be useful in predicting late effects of oncological treatment (19) but the endogenous event-related potentials, which detect the neuronal electrical activity associated with cognitive processing, seem to be more promising and encouraging as earlier studies suggested (20). These diagnostic methods are known to give objective information about both attention-dependent and independent central auditory processing with quite simple and inexpensive test arrangements.

According to our best knowledge, the presented data constitute the largest report about the implementation of event-related potentials in childhood ALL population. As we showed in our study, abnormalities in screening assessment of P300 potential were detected in more than a quarter of ALL survivors. Moreover, due to the inclusion of ALL patients treated with different protocols, a significant effect of the type of treatment on the nature of neuropsychological disorders in endogenous evoked potentials was observed. The analyzed protocols contribute to the prolongation of latency and reaction time of P300 potential. In turn, the use of therapeutic protocols quite similar in terms of used chemotherapy regimens but containing radiotherapy reduces its amplitude. These abnormalities can be used to provide a more accurate characterization of subtle and subclinical P300 potentials changes in childhood ALL survivors.

The endogenous potentials analyzed in current study are the result of changes in the electrical voltage associated with

information processing. They do not depend directly on the type of stimulus but on thinking processes and are classified as long-latency potentials constituting an electrophysiological indicator of cognitive processes (10). The P300 potential is determined by the positive wave with the highest amplitude recorded in the central-parietal midline leads in response to the processing of the auditory or visual stimulus. Stimulation with two distinct acoustic stimuli (oddball paradigm) is commonly used. The P300 wave arises after 300-800 msec. This wave occurs when the stimulus recognition is associated with a high level of subjective uncertainty and is a measure of the degree of attention devoted to a particular cognitive task. It is assumed that it is generated in the hippocampus and in the temporal and parietal lobes of the cerebral cortex (21).

Among the greatest advantages of neurophysiological techniques are their high sensitivity, non-invasiveness and the ability to repeat them at relatively low costs. They are an objective although non-specific neurological diagnostic tool. Endogenous potentials are widely used in clinical practice, in particular in the diagnosis of oligosymptomatic disease processes, mainly dementia syndromes (22). Their serial execution also allows to track the dynamics of the disease process and monitor the treatment; therefore they are helpful in determining the prognosis.

However, the usefulness of event-related potentials in the diagnosis and monitoring of adverse effects of childhood ALL treatment has not been sufficiently understood yet. As already mentioned, event-related potentials reflect the synchronized post-synaptic potentials generated by the depolarization of neurons, primarily the large pyramidal cells of the cerebral cortex. Its latency is a measure of the time needed for the cognitive processes preceding the cognitive assessment of the task situation, while the wave amplitude defines the involvement of cognitive structures. The changes observed by us indicate slower and more effortful target detection. Prolonged latency and a reduction in the amplitude of the P300 potential have already been shown in ALL survivors. However, all previous studies have been conducted on small groups of patients. P300 latency has been found to peak later and to have a smaller amplitude in childhood cancer survivors (20,23). However, a study by Lähteenmäki *et al* (20) was performed on a heterogeneous group of only 19 cancer survivors, in which there were 11 patients with ALL. In turn, Uberall *et al* included only 13 long-time ALL survivors in their study (23). Our results are also consistent with the results by Sato *et al* (24) who showed a significant increase in P300 latency in 33 patients treated with chemotherapy and radiotherapy compared to patients treated with chemotherapy alone and to the control group. Moore *et al* also made similar observations on an equally large group of childhood cancer survivors (25). Järvelä *et al* demonstrated the usefulness of P300 potentials in monitoring of central nervous system toxicity of ALL therapy in 27 patients. They showed a relationship between progressive deterioration of mental performance and prolongation of the peak latency as well as poorer enhancement of P300 amplitude after treatment (26). The previous observations presented above have also been confirmed by recently published preliminary results by Brace *et al* (13). Decreased amplitude of particular P300 components were observed in the analyzed small group of 8 ALL survivors treated exclusively with chemotherapy protocols.

Our study may also have potential therapeutic implications in the future. N-methyl-D-aspartate (NMDA) channels have a central role in the generation of event-related potentials (27). Differences in particular parameters of P300 potentials between ALL survivors and controls are consistent with altered neurotransmission through NMDA receptors (28). Recent preclinical study has revealed that memantine, non-competitive NMDA receptor antagonist, reduces the incidence of cognitive deficits in rats treated with intrathecal methotrexate (28). Memantine has also shown promising effects in randomized trial among adults treated with cranial radiation for brain tumors (29). Potentially, a group of patients with subtle neurocognitive dysfunction identified on the basis of screening with P300 event-related potentials can therefore experience the benefits of prophylactic use of NMDA antagonists. Such behavior may protect this selected group of patients from the development of symptomatic cognitive impairment. However, large randomized trials using NMDA antagonists in patients with childhood ALL are necessary to confirm this hypothesis.

Our study has several limitations. First, our study compared different protocols previously used in clinical practice. However, it was our deliberate intention. Thanks to this it is possible to study the impact of radiotherapy withdrawn from many protocols currently used in ALL on P300 potentials. Second, neuroimaging and neuropsychological correlations with neurophysiological results were not performed. However, the purpose of our study was only to evaluate the value of electrophysiological P300 potentials changes. The performed neurophysiological studies informed about maintaining the functional integrity of the nervous system. None of the patients exceeded the 5% margin of uncounted discriminating stimuli which indicates the correct concentration of attention. Third, genetic methods, which are increasingly used in the diagnosis of cognitive disorders in the pediatric population, have not been used (30).

As we did not study the neurological status of the patients at diagnosis, we could not prove the unambiguous cause of observed changes in P300. In case of primary localization all symptoms usually resolve after therapy. Therefore the observed changes were most likely consequences of therapy. Other limitation was lack of psychological assessment in the study protocol.

In conclusion, endogenous P300 event-related potentials may be useful in screening assessment of ALL survivors. The type of treatment protocol significantly modulates the individual parameters of the registered P300 potentials. Understanding with the analysis of event-related potentials how ALL survivors brain responses are affected post-treatment will elucidate the type of the cognitive deficits and provide insights into new potential targets for intervention or prevention strategies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SK and SS contributed to the study concept and design. SK, KK, AGe, OG and SS performed diagnostic tests and collected relevant clinical data. SK, KK and AGr conducted statistical analysis and wrote sections of the manuscript. SK and SS critically revised the article. SK and SS confirm the authenticity of all the raw data. All authors were responsible for the integrity and accuracy of the data and approved the submitted version. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol complied with the Declaration of Helsinki and was approved by the Jagiellonian University Medical College Ethics Committee (consent no. KBET/131/B/207). All parents, and patients over 16 years of age signed written informed consent before inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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