Attention and memory impairments in pediatric patients with cystic fibrosis and inflammatory bowel disease in comparison to healthy controls

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ABSTRACT

The main aim of the study was to analyze and compare attention and memory performance in pediatric patients with cystic fibrosis (CF), inflammatory bowel disease (IBD) and in healthy controls. 28 patients with CF, 30 patients with IBD and 30 healthy subjects took part in the study (all in age range of 7–17). All subjects were in intellectual norm. To analyze the functioning of attention, the d2 Test of Attention by Brickenkamp (d2 test) was applied. Memory performance was assessed using the Benton Visual Retention Test (BVRT) and the Trial of 10 words. The CF and IBD groups committed significantly more errors in the d2 test than the healthy controls. The CF group also had significantly higher fluctuation rates and received significantly lower scores in overall concentration performance than the control group. Patients with CF made more mistakes and had fewer correct memory projections in BVRT than the healthy controls. Patients with IBD committed significantly more errors in BVRT than the control group. Patients with CF and IBD also got significantly lower scores in the Trial of 10 words than the control group. Pediatric patients with CF and IBD performed more poorly than the healthy controls on attention and memory tests. More distinct cognitive impairments were observed in the CF group. Further research is needed to find the underlying mechanisms and clinical and/or functional significance of observed cognitive deficits.

Significance of this study

What is already known about this subject?

- Deficits in cognitive functioning have been identified to accompany a wide range of chronic illnesses. There are very few papers on cognitive functioning in cystic fibrosis (CF) or inflammatory bowel disease (IBD) but most of them concentrate on adult patients.
- Difficulties in handling verbal material and significantly lower verbal IQ than non-verbal IQ scores have been observed in adult patients with IBD. Memory deficits have been found in adolescent and adult patients with IBD.
- CF has been associated with deficits in memory, attention and executive function in adult patients. Memory deficits have been found in pediatric patients with CF and vitamin E deficiencies.

What are the new findings?

- Pediatric patients with CF and IBD performed more poorly than the healthy controls on attention and memory tests. More distinct cognitive impairments were observed in the CF group.
- The CF group also had significantly higher fluctuation rates and received significantly lower scores in overall concentration performance than the control group. Patients with CF made more mistakes and had fewer correct memory projections in Benton Visual Retention Test (BVRT) than the healthy controls.
- Patients with IBD committed significantly more errors in BVRT than the control group. The patients with CF and IBD also got significantly lower scores in the Trial of 10 words than the control group.

INTRODUCTION

Deficits in cognitive functioning have been identified to accompany a wide range of chronic illnesses including chronic kidney disease, lactose intolerance, chronic heart failure, diabetes mellitus, systemic lupus erythematosus, hepatitis C and chronic fatigue syndrome.[1–7] Cognitive impairments have also been found in chronically ill children and adolescents.[8–11] Cognitive dysfunction in chronic illnesses may be subtle and difficult to find, and the underlying mechanisms are yet to be fully determined. There are several hypotheses that have been proposed to explain cognitive deficits in chronically ill patients including: the impact of depression and anxiety that often occur in chronic illnesses, negative side effects of medication used in the treatment, and the disease process itself that may lead to neuropsychological impairments.[2]

Cystic fibrosis (CF) and inflammatory bowel disease (IBD) share many clinical similarities. Both diseases are chronic and occur in children. For both groups of patients, there is often a necessity for long-lasting and intensive

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Significance of this study

How might these results change the focus of research or clinical practice?

- The research shows the importance of cognitive assessment in chronically ill pediatric patients. Even seemingly minor cognitive deficits may have significant negative impact on patients' school performance, compliance with therapeutic regimen and the quality of social interactions. In this context, an early neuropsychological intervention could lower the risk of future complications.

pharmacotherapy and hospitalization. In both diseases, there are many gastrointestinal symptoms and systemic manifestations. Both diseases are also linked with a higher risk of disturbances in the physical development in children and adolescents. States of malnutrition, dehydration, deficiencies of vitamins and trace elements that often occur in CF and IBD have been associated with deficits in cognitive development.[12–15] However, despite the similarities, there is no doubt that CF is the illness with much more serious consequences affecting the functions of the patient. First of all, CF manifests itself from birth and its symptoms are progressive, while IBD develops later in life and is usually characterized by periods of remission. Furthermore, CF is marked by severe chronic respiratory symptoms which have been linked with cognitive deficits in other diseases.[11 16–19] Patients with CF are also at a greater risk of secondary complications or comorbidities such as diabetes, osteoporosis and cirrhosis of the liver.

There are very few papers on cognitive functioning in CF or IBD.[2 16 20–27] Most of them concentrate on adult patients. CF has been associated with deficits in memory, attention and executive function in adult patients.[21] Similar impairments have been found among patients with CF suffering from end-stage pulmonary disease awaiting lung transplantation.[16 22] Koscik *et al*[24] found memory deficits in pediatric patients with CFwith vitamin E deficiencies. Executive function deficits were also found in a recent study on cognitive functioning in adult patients with CF with and without cystic fibrosis-related diabetes.[27] Difficulties in handling verbal material and significantly lower verbal IQ than non-verbal IQ scores have been observed in adult patients with IBD.[2 25] Memory deficits have been found in adolescent and adult patients with IBD.[23 26]

The main aim of the present study was to examine and compare the functioning of memory and attention in pediatric patients with IBD or CF. A healthy control group was used for comparison. As mentioned in the previous paragraph, there have been reports of memory deficits in both diseases and CF has been linked with attention dysfunctions. So far, to our best knowledge, there have not been any reports of attention deficits in patients with IBD. It was hypothesized that both patient groups would perform more poorly than the healthy controls on memory and attention tests, and given the more severe pathology of CF (especially the presence of respiratory symptoms), the CF group would have more severe cognitive dysfunctions than the IBD group.

MATERIAL AND METHODS

The study project was carried out using three groups of subjects—two patient groups and a control group. The subjects in both patient groups were patients of the Karol Jonscher University Hospital in Poznan between October 2015 and May 2016. We used quota sampling. It was decided that 50% of the subjects included in the study would attend primary school, 25% middle school and 25% high school. In every educational stage, the sex distribution had to be equal. The inclusion and exclusion criteria are given in the below sections.

Inclusion criteria for the CF group

- being diagnosed with CF within first 12 months after birth;
- pancreatic insufficiency;
- between the age of 7 and 18 years;
- no other conditions that could affect the study results, such as thyroiditis, diabetes, attention-deficit/hyperactivity disorder (ADHD), depression, epilepsy and so on;
- attending public school and not having an individual teaching course;
- consent of a patient, legal guardian and the main doctor for participating in the study.

Exclusion criteria for the CF group

- being diagnosed with CF after first 12 months after birth;
- without pancreatic insufficiency;
- below the age of 7 years or above the age of 18 years;
- suffering from other conditions that could affect the study results, such as thyroiditis, diabetes, ADHD, depression, epilepsy and so on;
- not attending public school or having an individual teaching course;
- lack of consent of the patient, the legal guardian or the main doctor for participating in the study.

Inclusion criteria for IBD group

- being diagnosed with Crohn's disease or ulcerative colitis (UC) diagnosed not more than 5 years before the study visit;
- between the age of 7 and 18 years;
- no other conditions that could affect the study results, such as thyroiditis, diabetes, ADHD, depression, epilepsy and so on;
- attending public school and not having an individual teaching course;
- consent of the patient, the legal guardian and the main doctor for participating in the study.

Exclusion criteria for IBD group

- being diagnosed with Crohn's disease or ulcerative colitis diagnosed more than 5 years before the study visit;
- below the age of 7 years or above the age of 18 years;
- suffering from other conditions that could affect the study results, such as thyroiditis, diabetes, ADHD, depression, epilepsy and so on;

- not attending public school or having an individual teaching course;
- lack of consent of the patient, the legal guardian or the main doctor for participating in the study.

The subjects in the control group (C) were matched for educational stage and sex. They were recruited in April and May 2016 from three public schools (one primary, one middle and one high school) in Poznan that were randomly chosen from all public schools in the city. The inclusion and exclusion criteria were as follows:

Inclusion criteria for the control group

- no serious, chronic or acute health problems;
- between the age of 7 and 18 years;
- not having an individual teaching course;
- consent of the subject and the legal guardian for participating in the study.

Exclusion criteria for the control group

- chronic or acute health problems;
- having an individual teaching course
- lack of consent of the subject or the legal guardian for participating in the study.

The first patient group constituted 30 children and adolescents with IBD (15 male and 15 female, 16 with Crohn's disease and 14 with ulcerative colitis) with the mean age 13.13 (SD=3.31, range 7–17). The mean time from the diagnosis was 2.4 years (SD=1.29, range 1–4). The second patient group consisted of 28 pediatric patients with CF (14 male and 14 female) with the mean age 12.5 (SD=3.42, range 7–17). The control group included 30 subjects (15 male and 15 female), with mean age 12.93 (SD=3.25, range 7–17). Age differences between groups were not significant ($F(2, 85)=0.273$; $p=0.762$). Subjects' age distribution is shown in table 1. All patients with CF during the study were undergoing planned prophylactic antibiotic treatment. Patients with IBD were in active stadium of the disease and were medicated with glucocorticoids. Cognitive tests were conducted during first 14 days of hospitalization in a separate and quiet room.

To assess the functioning of attention, the d2 test was used. The d2 test is a tool for measuring different aspects of non-verbal attention, relatively independent of general intelligence.[28 29] The d2 test requires the ability to properly select visual stimuli as important or unimportant at a fast pace, without being distracted.[28] The d2 test consists of a form with 14 lines, each containing 47 characters—the letters 'd' and 'p', with different number of dashes above or below them. Respondents are to cross out only 'd's' with two dashes (two dashes at the top or two at the bottom of the letter, or one on top and one at the bottom of the letter). The subject has 20 s for each line of characters.

Table 1 Subjects' age distribution

Age range	CF (n=28)	IBD (n=30)	C (n=30)	Total (n=88)
7–10	10 (35.7%)	7 (23.3%)	8 (26.7%)	25 (28.4%)
11–14	7 (25%)	10 (33.3%)	10 (33.3%)	27 (30.7%)
15–17	11 (39.3%)	13 (43.3%)	12 (40%)	36 (40.9%)

C, control group; CF, cystic fibrosis; IBD, inflammatory bowel disease.

To analyze visual memory, BVRT was applied. BVRT is used in the diagnosis of visual perception, visual memory and visual-constructive abilities.[30] The test consists of 10 cards with the models of geometric figures (one, two or three figures), and 10 blank cards of the same dimensions, which are used to replicate the patterns with a pencil. The subject is to watch each card with geometric figures for 10 s, and then the subject is asked to immediately reconstruct its pattern from memory.

For the analysis of auditory memory, the Trial of 10 words was conducted. The test allows for the examination of direct and deferred auditory memory, and the durability of learning of verbal material. This test is a clinical experiment, and has a standardized procedure. The subject listens to a list of 10 words read by the researcher (at a rate of one word per second), and after that the subject repeats all the words he or she remembers from the list. This reading repeating cycle is done five times. Then, for the purpose of distraction, a list of other 10 words is read, which the subject has to memorize and repeat, then the person is asked to repeat the original list of words without re-reading it. Finally, after 30 min, the subject is asked to recall words from the initial list (also without rereading) for the last time.

General intellectual performance level (fluid intelligence) was assessed with Raven's Progressive Matrices in Standard Version (Raven).

The study project received a positive opinion from the Bioethics Committee at Poznan University of Medical Sciences. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation.

IBM SPSS Statistics V.21.0 for Windows was used for statistical analyses. The data were analyzed using analysis of variance (ANOVA) with post hoc Duncan's test and univariate covariance analysis (ANCOVA). Statistical significance was set at $p<0.05$ for all analyses.

RESULTS

There were not any significant differences between groups in intelligence level measured with Raven—$F(2, 85)=0.211$; $p=0.81$. The highest mean was received by the control group (65.53 centiles, SD=25.74, range 11–98), the mean for the IBD group amounted to 62.73 centiles (SD=27.26, range 11–97), and the CF group received the lowest mean (60.93, SD=28.85, range 13–97).

ANOVA showed significant differences between groups in the d2 test (total number of errors, percentage of errors, fluctuation rate and concentration performance), BVRT (number of correct reproductions and total number of errors) and in the Trial of 10 words (average after five attempts, after distraction and after 30 min). Post hoc Duncan's test was used to determine which groups significantly differ from each other at $p<0.05$ (table 2). ANCOVA with indicators of the d2 test, BVRT and trial of 10 words as dependent variables and with age and level of intelligence as covariates, showed that group still had a significant impact on every one of the analyzed indicators (table 3).

The CF and IBD groups had significantly more errors in the d2 test than the control group ($F(2, 85)=4.3$; $p=0.017$). The CF and IBD groups also had higher percentage of

Table 2 Significant group differences in the d2 test, BVRT and trial of 10 words between CF (n=28), IBD (n=30) and C (n=30)

	CF Mean (SD)	IBD Mean (SD)	C Mean (SD)	*F*(2, 85)	p Value	Post hoc Duncan's test (p<0.05)
d2: total number of errors	28.5 (27.47)	27.03 (23.93)	13.03 (13.9)	4.3	0.017	CF, IBD > k
d2: percentage of errors	6.89 (5.9)	6.31 (5.12)	3.05 (3.5)	5.22	0.007	CF, IBD > k
d2: fluctuation rate	15.75 (5.14)	14.33 (5.58)	12.37 (3.16)	3.748	0.028	CF > k
d2: concentration performance	150.04 (45.2)	160.2 (48.25)	179.27 (40.82)	3.196	0.046	CF < k
BVRT: number of correct reproductions	6.57 (1.85)	7.07 (1.36)	7.73 (1.46)	4.029	0.021	CF < k
BVRT: total number of errors	5 (2.91)	4.17 (1.95)	2.87 (2.19)	5.993	0.004	CF, IBD > k
Trial of 10 words: average after five attempts	7.69 (0.78)	7.64 (0.9)	8.13 (0.61)	3.636	0.031	CF, IBD < k
Trial of 10 words: after distraction	7.79 (1.71)	8.23 (1.55)	9.1 (1.13)	5.999	0.004	CF, IBD < k
Trial of 10 words: after 30 min	8.04 (1.48)	8.2 (1.37)	8.97 (1.1)	4.155	0.019	CF, IBD < k

BVRT, Benton Visual Retention Test; C, control group; CF, cystic fibrosis; d2 test, d2 Test of Attention by Brickenkamp.

errors than the controls ($F(2, 85)=5.22$; p=0.007). The CF group had significantly higher fluctuation rate in the d2 test than the control group ($F(2, 85)=3.748$; p=0.028). The CF group also had significantly lower concentration performance in the d2 test than the controls ($F(2, 85)=3.196$; p=0.046). There were not any significant differences between groups in speed and accuracy of visual processing.

The CF group had significantly less correct reproductions in BVRT than the control group ($F(2, 85)=4.029$; p=0.021). The CF and IBD groups made more errors in BVRT compared with the controls ($F(2, 85)=5.993$; p=0.004).

The CF and IBD groups received significantly lower average of correct recalls after five attempts in the trial of 10 words than the control group ($F(2, 85)=3.636$; p=0.031). Compared with the control group, the CF and IBD groups also had lower averages of correct recalls in the Trial of 10 words after distraction ($F(2, 85)=5999$; p=0004) and after 30 min ($F(2, 85)=4155$; p=0019).

DISCUSSION

Attention is a complex cognitive function, which enables an individual to select out of the numerous stimuli the ones which are regarded in the given moment more significant or interesting, and hence devoting a bigger amount of the available resources of processing.[31] It is a cognitive filter closely related to other cognitive processes, primarily to the perception and memory, but also to the motivational-emotional processes. In this study, no significant differences were noticed between the groups in terms of the overall speed of perception and the general accuracy of perception assessed with the d2 test. The CF and IBD groups committed significantly more errors (quantitatively and in terms of percentage) than the healthy controls. The CF group also had significantly higher fluctuation rates than the control group, which may indicate a lesser level of performance consistency. Furthermore, the CF group received significantly lower scores than the control group within the scope of the overall concentration performance. Compared with the control group, subjects of the CF group had reduced attention span, lesser work stability requiring mental alertness, the subjects also committed more mistakes of omitting and incorrect crossing outs. In recent studies, only Maddrey *et al*[21] pointed the presence of attention deficits among the patients with CF. However, the study was conducted on patients over the age of 17. The subjects with IBD committed more mistakes of omitting and incorrect crossing outs than the healthy subjects. To our knowledge, it is the first report that shows possible deficits in attention in patients with IBD.

Memory is described as a process of information processing, which consists of: encryption which enables the conversion of stimuli into memory engrams, storage, in which there is a modification of memory records and the reconstruction of the content stored in the memory in the form of recall or recognition.[32] Efficient memory is a prerequisite for learning processes, is also the basis for the attention and awareness, thinking and communication processes.[31 33] In this study, memory processes were analyzed for the visual modality on non-verbal material (BVRT), as well as for the auditory modality for verbal material (the Trial of 10 words).

Table 3 Univariate covariance analysis with indicators of BVRT, the d2 test and Trial of 10 words as dependent variables

	Group			Age			Intelligence (Raven)		
	F(2, 83)	p Value	η^2	*F*(1, 83)	p Value	η^2	*F*(1, 83)	p Value	η^2
d2: total number of errors	4.042	0.021	0.089	0.130	0.72	0.002	2.065	0.155	0.024
d2: percentage of errors	4.819	0.01	0.104	1.586	0.211	0.019	2.316	0.132	0.027
d2: fluctuation rate	3.473	0.036	0.077	4.032	0.048	0.046	0.167	0.684	0.002
d2: concentration performance	4.728	0.011	0.102	102.493	0.001	0.552	30.946	0.001	0.272
BVRT: number of correct reproductions	4.572	0.013	0.099	45.225	0.001	0.353	4.701	0.033	0.054
BVRT: total number of errors	7.331	0.001	0.15	44.355	0.001	0.348	2.477	0.119	0.029
Trial of 10 words: average after five attempts	3.543	0.033	0.079	6.890	0.010	0.077	8.448	0.005	0.092
Trial of 10 words: after distraction	5.838	0.004	0.123	14.001	0.001	0.144	4.092	0.046	0.047
Trial of 10 words: after 30 min	3.809	0.026	0.084	4.457	0.038	0.051	3.590	0.062	0.041

BVRT, Benton Visual Retention Test; d2 test, d2 Test of Attention by Brickenkamp.

Patients with CF made more mistakes in BVRT and had fewer correct memory projections than the healthy subjects. Compared with the control group, the CF group got significantly lower average of correct recalls in the Trial of 10 words after five attempts, after distraction and after 30 min. This may indicate a reduced ability to learn and retain information in patients with CF. Until now, the presence of non-verbal and verbal memory deficits has been reported among patients diagnosed with CF over 17 years of age, as well as among patients with CF diagnosed with vitamin E deficiencies.[21 24] Verbal memory deficits were also observed among patients with CF awaiting lung transplant.[22] Our results stand in opposition to the existing studies on memory in pediatric patients with CF (5–8 and 10–16 years old), which showed no deficits in verbal and non-verbal memory.[4 20]

The IBD group committed significantly more errors in BVRT than the healthy controls, but there was no significant difference in the number of correct reproductions. To our best knowledge, these are the first reports of possible visual memory deficits in patients with IBD. The IBD group which received significantly lower scores than the healthy subjects in the Trial of 10 words for each of the indicators examined (average correct recalls after five attempts, after distraction and after 30 min) may reflect their reduced ability to learn and retain new verbal material. This corresponds with the existing studies on verbal memory among patients with the IBD.[23 26] Difficulties in handling verbal material were also observed in the study on intelligence of adult patients with IBD, in which the verbal IQ was significantly lower than the non-verbal IQ.[2 25]

Both patient groups in our study performed more poorly than the healthy controls on attention and memory tests. More distinct dysfunctions were observed in the CF group, as was hypothesized given the more severe pathology of cystic fibrosis. The mechanisms underlying observed dysfunctions are yet to be fully understood. Patients with CF and pancreatic insufficiency are at greater risk for fat-soluble vitamin deficiency, especially during infancy and in prior study Koscic *et al*[24] linked cognitive deficits in pediatric patients with CF and prolonged vitamin E deficiencies. Cognitive dysfunctions have also been found in many other diseases with respiratory symptoms, for example, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea.[16–19 34] One of the possible explanations of cognitive deficits in pulmonary diseases is associated with neuronal damage meditated through hypoxia and/or hypercapnia.[35 36] Both hypercapnia and hypoxia are often observed in patients with CF which may be a potential underlying mechanism of observed cognitive dysfunctions. Other hypothesized cause of neural symptoms in CF relate to the CF transmembrane conductance regulator (CFTR) gene which is foundational in the pathology of the disease. CFTR is also present and expressed in human brain which may explain the neuropsychological symptoms in patients with CF.[37 38] However, the potential causation is yet to be understood. As for patients with IBD, there are also several hypothesis regarding the observed cognitive deficits in this group. Cognitive impairments have been associated with systemic inflammation in Crohn's disease, and elevations in serum titers of cytokines with longer response time on cognitive tasks in elderly population.[39 40] Experiments on rodents have shown that inflammation of the colon leads to an upregulation of inflammatory activity in microglia of the hippocampus that may result in postsynaptic response dysfunctions.[41] Whether such effects occur in humans is yet to be determined. One of the proposed explanation of cognitive dysfunctions concentrates on the negative side effects of the medication used in IBD treatment. It is well known that glucocorticoids may affect cognitive functioning.[42] All our patients with IBD were in the active state and were on glucocorticoids. Unfortunately, the total time of glucocorticoids exposure was not available. Concurrent conditions like depressive and anxiety symptoms, anemia, fatigue, poorer sleep quality are also considered as important factors that may influence cognitive performance in IBD.[26 39 43 44]

The study has several limitations. First, only 28 CF, 30 IBD and 30 control subjects were recruited in a relatively broad age range (7 to 17 years old), which is associated with dynamic neural development. Although, the study groups did not differ in terms of mean age, educational stage or sex, it would be important to design a study with larger group samples in different development stages that would allow for better generalization of the results to the patient population. Additionally, longitudinal studies are needed for monitoring cognitive changes across time. Another limitation is that the control subjects were recruited from schools from the main city in the region while patient precipitants came also from small towns or rural areas. Furthermore, control of the diseases severity and treatment (eg, glucocorticoids exposure in IBD and respiratory functioning in CF) would be necessary to find the underlying mechanisms of the observed deficits.[35–42] Another limitation is that there may be some potential confounders, that is, fatigue, sleep deprivation, anxiety and depression symptoms, anemia, acute stressful life events (eg, divorce of parents), that should be taken into account as they may influence cognitive performance.[26 39 43–46] It would also be beneficial to match the subjects (especially the control group) for other demographic factors (like parents' education, income estimates, place of habitation). Moreover, these factors might improve the modeling of cognitive performance in the studied population. Further limitation reflects the chronic relapsing nature of IBD, in which activity varies over time. It is probable that in IBD, cognitive deficits may only be present when symptoms are active. It would be interesting to see how recently diagnosed patients perform in comparison to patients diagnosed, for example, more than 5 years ago. It would also be noteworthy to compare CD and UC subgroups. Unfortunately, the relatively small sample size did not allow for that. A final limitation is that only certain features of cognitive function were examined. It is possible that other specific forms of attention, memory, motor function, perception, executive function or language that were not assessed in this study could be affected.

The clinical significance of our finding and its possible impact on patients with CF and IBD school performance and other aspects of life is unclear, warranting further research. However, it is important to state that even seemingly minor cognitive deficits may have significant negative impact on school performance, compliance with therapeutic regimes and the quality of social interactions. In this context, an early neuropsychological assessment and intervention could lower the risk of future complications.

CONCLUSION

Pediatric patients with CF and IBD performed more poorly than the healthy controls on attention and memory tests. More distinct cognitive impairments were observed in the CF group. Further research is needed to find the underlying mechanisms and clinical and/or functional significance of observed cognitive deficits.

Contributors BP and EM conceived the study. BP collected the data and evaluated the data in collaboration with EM, MS-K and WS. BP, MS-K, EM and WS participated in literature search. BP in collaboration with EM performed data analysis, data interpretation, and wrote the manuscript. MS-K and WS contributed substantially to the manuscript revision. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Ethics approval Approval by the Bioethics Committee at Poznan University of Medical Sciences was obtained and this study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The participation in the study was preceded by obtaining the consent from the participants and their legal parents (guardians).

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