

Executive function in pediatric patients with cystic fibrosis, inflammatory bowel disease and in healthy controls

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Abstract. – OBJECTIVE: The main aim of this study was to analyze and compare executive function performance in pediatric patients with cystic fibrosis (CF), inflammatory bowel disease (IBD) and in healthy controls.

PATIENTS AND METHODS: 28 patients with CF, 30 patients with IBD and 30 healthy participants took part in the study (all in the age range of 7-17). All participants were in the intellectual norm. The Wisconsin Card Sorting Test (WCST) was applied to assess executive functions.

RESULTS: The CF group received significantly ($p < 0.05$) poorer scores than the control and IBD groups in the following WCST indicators: Number of trials administered, Total number of errors, Perseverative errors, Non-perseverative errors, Percent of conceptual level responses, Trials to complete the first category. The IBD group was not significantly different from the control group in any of the WCST indicators.

CONCLUSIONS: To our best knowledge, results of this study are the first report of the presence of executive function deficits among pediatric patients with CF. It is also the first study that describes the performance of the executive function in IBD pediatric patients, and the first that compares cognitive functioning between CF and IBD patients.

Key Words:

Cystic fibrosis, Inflammatory bowel disease, Executive function, Cognitive functions, Neuropsychology, Children, Adolescents.

Introduction

Many chronic illnesses are associated with impaired cognitive functioning (e.g. chronic kidney disease, chronic heart failure, type 2 diabetes, hepatitis C, chronic fatigue syndrome), although the underlying mechanisms are not fully known¹⁻⁵. Chronic illness heavily determines a child's psychosocial development, including the cognitive

development^{2,6}. Both Cystic Fibrosis (CF) and Inflammatory Bowel Disease (IBD) are chronic illnesses, in which there are numerous symptoms related to the functioning of the digestive system, including parenteral symptoms and systemic dysfunctions. Both diseases are associated with higher risk of physical development disorders among children and adolescents. Clinical manifestations include disorders of the body's physiological balance (states of malnutrition and dehydration, deficiency of vitamins and trace elements), a weak increase in the body weight and height, as well as delayed pubescence. These symptoms are associated with the development and efficiency of the central nervous system (CNS), and thus can affect the cognitive functioning of patients⁷⁻¹¹. For both diseases a long lasting and often intensive hospital treatment is necessary. In spite of many similarities, CF has a much greater impact on the functioning of a patient. CF is a genetic disease that manifests itself from birth, while IBD develops in the course of life. CF is associated with numerous symptoms of the respiratory and reproductive systems and with a higher risk of serious complications such as secondary diabetes mellitus and cirrhosis of the liver. Furthermore, CF symptoms are progressive, while in IBD there are often long periods of remission.

Cystic fibrosis is a congenital systemic disease, inherited as an autosomal recessive disorder. The disease is caused by the mutations of the cystic fibrosis transmembrane conductance regulator gene (CFTR), encoding a protein responsible for the formation of chloride channels in the cell membrane. Faulty construction of the protein leads to disturbance in the flow of sodium and chloride ions through epithelial cells, resulting in an increased viscosity and density of secretions. As a consequence, there are functional and struc-

tural disorders of the exocrine glands and systems directly related, especially respiratory and digestive^{12,13}.

Cystic fibrosis is one of the most common genetic diseases. The highest incidence of CF occurs in Caucasians. In 2008 Farrell¹⁴ estimated the occurrence of CF in the European Union at the level of 0.737/10,000 – from 0.104/10,000 in Latvia to 2.98/10,000 in Ireland. In the United States, the incidence of CF is estimated at 1:3,500, while in India it is 1:40,000-100,000 and in Japan 1:100,000-300,000¹⁵. For Poland, the occurrence of CF is 0.256/10,000 and the incidence is estimated at 1:5,000¹⁴.

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases of the gastrointestinal tract characterized by periods of exacerbation and remission. The main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC), but there are also other less common conditions such as nonspecific colitis, Behcet's disease and collagenous colitis¹⁶. The etiology of IBD is not well understood yet. It is probably multifactorial in origin, and the key role is attributed to the interaction of genetic, environmental and immunological factors¹⁷⁻¹⁹.

The highest incidence rates of IBD occur in Western Europe and North America, among Caucasians, in countries with high levels of industrialization and high socioeconomic status²⁰⁻²³. The incidence of UC in North America ranges from 37 to 246/100,000 inhabitants, and the prevalence of CD range from 26 to 201/100,000^{20,23}. In Europe, the incidence of UC is estimated at 21 to 294/100,000, while for the CD this ratio ranges from 8 to 214/100,000^{20,23}. The incidence rates of IBD in developed countries is now relatively stable and reaches from 1.5 to 20/100,000 per habitat within a year for UC and 0.7 to 14.6/100,000 for CD^{20,21,23}. IBD usually occurs in the third decade of life, but in recent years there has been a reduction in the average age at the time of diagnosis and an increased incidence of IBD among children and adolescents. It is estimated that from 7 to 20% of all IBD patients are pediatric patients^{22,23}.

There are few papers on cognitive functioning in CF and IBD (e.g. ^{1,24-31}). IBD has been associated with verbal memory deficits^{29,30}. Difficulties in handling verbal material were also observed in studies on intelligence in adult IBD patients in which verbal IQ was significantly lower than non-verbal IQ^{1,28}. Deficits in memory, attention and executive function were observed in adult

patients with CF²⁵. Similar deficits were observed in patients with CF suffering from end-stage pulmonary disease, awaiting lung transplantation^{26,31}. Memory deficits were also observed amongst pediatric CF patients with vitamin E deficiencies²⁷. Impairments in executive function were also found in a recent study on cognitive functioning in adult CF patients³².

The main aim of this study was to analyze and compare executive function performance in pediatric patients with CF and IBD. As indicated in the previous paragraph, executive function deficits have been found in adult CF patients. Other diseases with respiratory symptoms have also been associated with executive function impairments³³⁻³⁵. Based on previous studies and knowledge of specific disease pathology, the following hypotheses were developed:

Given the early onset of the disease and its systemic pathology (especially respiratory) and that there are reports showing executive function deficits in adult CF patients, we expected that CF patients would perform more poorly than the control and IBD groups on measures of executive functions.

Given that there aren't any reports on executive function deficits in IBD and the duration of the disease in children is relatively short, and that there aren't any respiratory symptoms present in IBD, we expected that IBD group wouldn't significantly differ from the control group in the performance of executive functions.

Patients and Methods

The research project received a positive opinion from the Bioethics Committee at Poznan University of Medical Sciences (PUMS). 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 and with the Helsinki Declaration of 1975, as revised in 2008.

The study included three groups – two patient groups and the control group. The first patient group constituted 28 children and adolescents (14 male and 14 female) with CF (mean age: 12.5, SD = 3.42, range 7-17). The second patient group included 30 participants with IBD (15 male and 15 female, 16 with CD and 14 with UC). The mean age for the IBD group was 13.13 (SD = 3.31, range 7-17). The participants in both groups were patients of the Karol Jonscher Uni-

versity Hospital at PUMS. During the study, all IBD patients were in the active stadium of the disease, and they were medicated with glucocorticoids. CF patients were undergoing planned prophylactic antibiotic treatment. All tests were conducted during first 10 days of hospitalization. None of the participants suffered from other medical conditions that could affect the study results, such as thyroiditis, epilepsy, ADHD etc. All participants attended public schools. Participation in the research was conditioned on the consent of the patient, patient's legal guardian and the main doctor. The control group (k) consisted of 30 healthy participants (15 male and 15 female) and had a mean age of 12.93 (SD = 3.25, age range 7-17). The subjects in the control group were students of Poznan public schools. The participation in the study was preceded by obtaining the consent of the tested persons and their legal guardians. The analysis of variance (ANOVA) showed that age differences between groups weren't significant ($F(2, 85) = 0.273$; $p = 0.762$).

To analyze executive functions the Wisconsin Card Sorting Test (WCST) was applied. WCST is considered to be a tool for measuring executive function which supervises, control and directs the cognitive activity of a person³⁶. General intellectual level (fluid intelligence) was measured with Raven's Progressive Matrices in Standard Version (TMS-K).

Statistical Analysis

Statistical analyses were carried out with IBM SPSS Statistics version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). 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

The analysis of variance (ANOVA) showed that there weren't any significant differences between groups in Raven's Progressive Matrices intelligence test – $F(2, 85) = 0.211$; $p = 0.81$. The highest mean was received by the control group (65.53 centiles, SD = 25.74, range 11-98), and the CF group received the lowest mean (60.93, SD = 28.85, range 13-97). The mean for the IBD group amounted to 62.73 centiles (SD = 27.26, range 11-97).

The analysis of variance (ANOVA) showed significant differences between groups in the following WCST indicators: number of trials administered, total number of errors, Perseverative errors, non-perseverative errors, percent of conceptual level responses, trials to complete the first category. Post hoc Duncan's test was applied to determine which groups significantly differ from each other at $p < 0.05$ (Table I). Univariate covariance analysis (ANCOVA) with indicators of WCST 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 WCST indicators (Table II).

The CF group needed significantly more trials in WCST than the IBD and control groups – $F(2, 85) = 5.563$; $p = 0.005$. The CF group in comparison to the IBD and control groups had significantly more total errors ($F(2, 85) = 6.771$; $p = 0.002$), perseverative errors ($F(2, 85) = 4.317$; $p = 0.016$) and non-perseverative errors ($F(2, 85) = 5.743$; $p = 0.005$). CF patients needed significantly more trials to complete the first category of the test than IBD patients and the controls – $F(2, 85) = 5.896$; $p = 0.004$. The CF group also received a significantly lower percentage of responses on a conceptual level than the other two groups – $F(2, 85) = 5.372$; $p = 0.006$.

Table I. Significant group differences in WCST between CF (n=28), IBD (n=30) and k (n=30).

WCST	CF mean (SD)	IBD mean (SD)	k mean (SD)	F (2, 85)	p	Post-hoc Duncan's test ($p < 0.05$)
Number of trials administered	114.11 (14.68)	98.9 (18.92)	101.7 (20.38)	5.563	0.005	CF > IBD, k
Total number of errors	37.86 (16.52)	26.53 (14.5)	24.23 (13.99)	6.771	0.002	CF > IBD, k
Perseverative errors	20.71 (11.67)	15.1 (11.17)	12.93 (7.93)	4.317	0.016	CF > IBD, k
Non-perseverative errors	17.21 (8.59)	11.53 (6.92)	11.27 (6.96)	5.743	0.005	CF > IBD, k
Percent conceptual level responses	59.31 (15.01)	69.84 (13.51)	69.84 (13.59)	5.372	0.006	CF < IBD, k
Trials to complete first category	18 (9.06)	12.6 (3.58)	13.6 (5.34)	5.896	0.004	CF > IBD, k

Table II. Univariate covariance analysis with indicators of WCST as dependent variables.

WCST	Group			Age			Intelligence		
	F(2, 83)	p	η ²	F(1, 83)	p	η ²	F(1, 83)	p	η ²
Number of trials administered	5.770	0.005	0.122	26.489	0.001	0.242	26.393	0.001	0.241
Total number of errors	6.737	0.002	0.140	24.838	0.001	0.230	18.885	0.001	0.185
Perseverative errors	3.924	0.024	0.086	24.034	0.001	0.225	15.999	0.001	0.162
Non-perseverative errors	5.098	0.008	0.109	8.151	0.005	0.089	8.246	0.005	0.090
Percent conceptual level responses	4.993	0.009	0.107	17.547	0.001	0.175	17.857	0.001	0.177
Trials to complete first category	5.286	0.007	0.113	9.865	0.002	0.106	2.210	0.141	0.026

Discussion

Executive functions supervise, control and direct the cognitive activity of a unit. As the higher mental activities, they are associated with such skills as setting goals, abstract logical thinking, planning, taking into account the long-term consequences, initiating intentional actions, creating different possible alternative reactions, or modifying own activity in response to changing conditions. Executive functions are involved in virtually every human activity, not counting instinctive reactions or actions best automated and learned^{37,38}. This study indicates the existence of significant differences between studied groups in the area of executive function performance. The group of cystic fibrosis scored significantly poorer than the control and IBD groups in the following WCST variables: Number of trials administered, Total number of errors, Percent errors, Perseverative errors, Percent perseverative errors, Non-perseverative errors, Percent non-perseverative errors, Percent conceptual level responses, Trials to complete the first category. The IBD group was not significantly different from the control group in any of the WCST subtest which corresponds with previous studies. IBD has been linked with memory and verbal IQ deficits, however, there has been no evidence of executive function impairments, neither in pediatric nor adult patients^{1,28-30}.

The participants with CF committed more mistakes, they more frequently demonstrated perseveration and less frequently answered in accordance with logical and conceptual premises. These findings suggest the presence of reduced efficiency of executive functioning among patients with cystic fibrosis. Our findings correspond to those of other authors who researched this matter. Maddrey et al²⁵ observed

deficits in memory, attention and executive function in patients with CF over the age of 17. Similar deficits were observed in patients with CF suffering from end-stage pulmonary disease awaiting lung transplantation^{26,31}. Executive function deficits were also found in a recent study³² on cognitive functioning in adult CF patients with and without cystic fibrosis related diabetes. Executive function and other cognitive deficits have been found in other diseases with respiratory dysfunctions, e.g. chronic obstructive pulmonary disease, asthma, obstructive sleep apnoea^{33-35,39,40}. A neuronal damage mediated through hypoxia and/or hypercapnia is proposed to be one of the key mechanisms of cognitive dysfunctions in pulmonary diseases^{41,42}. Both hypoxia and hypercapnia are often present in CF patients which may be a potential underlying cause of observed deficits. Other possible mechanism of cognitive deficits in CF may be associated with CFTR gene which is fundamental in the pathology of the disease. CFTR is present and expressed in the human brain which may explain the neural symptoms in CF patients^{43,44}. However, the functions of CFTR in the human brain and its link with cognitive deficits is yet to be understood. Further research on the potential causation is warranted.

Conclusions

To our knowledge results of this study are the first reports of executive function deficits among children and adolescents with CF in relatively good health. Executive function impairments may lead to logical, conceptual and abstract thinking deficits, lower cognitive flexibility and reduced ability to change the current course of reasoning in response to changing circum-

stances³⁶. It is also stressed that even seemingly minor executive function deficits may have significant negative impact on the effectiveness in everyday life and the quality of social interactions^{37,38}. The clinical significance of our data and its possible impact on CF patients' school performance, compliance with therapeutic regimes, and on other aspects of life is unclear, warranting further research. 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. Control of the diseases severity (especially of respiratory functioning) would also be necessary to find the underlying causes of the observed deficits.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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