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Cognitive impairments in Polish children and adolescents with perinatal HIV infection

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Summary

Aim. The aim of the study was to assess the presence of cognitive impairments in children and adolescents with vertically transmitted HIV infection and to determine possible relationships with clinical and sociodemographic variables.

Method. The study included: 50 children with perinatal HIV infection aged 6–18 years (PHIV+), 24 healthy children perinatally HIV-exposed but uninfected (PHEU) and 43 healthy children of uninfected parents (HIV-nA). CANTAB Research Suite was used to assess cognitive impairments.

Results. In comparison with the HIV-nA group, the PHIV+ group scored significantly lower in shifting of attention, cognitive flexibility, use of feedback, and working memory. In comparison with the PHEU group, the PHIV+ group had significantly longer planning time while performing the task. The analysis of results for the 12–18 year-old age group revealed deterioration of cognitive functions in all tests of the PHIV+ children in comparison with the HIV-nA group. A higher logarithm of viral load at the start of the ARV treatment was associated with lower results in the use of feedback, shifting of attention, cognitive flexibility, and worse information processing.

Conclusions. Results of the research indicate deterioration of executive functioning in the PHIV+ group associated with longer duration of HIV neuroinfection and severity of infection before treatment.

Key words: HIV infection, cognitive dysfunctions, child and adolescent psychiatry

Introduction

In children and adolescents with perinatal HIV (human immunodeficiency virus) infection, cognitive functioning may be affected by fetal factors (HIV infection, medications taken by the mother, drugs, alcohol, malnutrition, and other infections and diseases), HIV course-related factors and environmental factors (cognitive and educational levels of the parents, socioeconomic status, the presence of illness, the experience of loss of a parent, etc.) [1]. In the majority of studies on perinatally HIV-infected (PHIV+) subjects, general intellectual functioning tests have typically been used as indicators of neurodevelopmental cognitive deficits. The general result of the examination of the intellectual level within population norm levels does not fully reflect the cognitive functioning [2, 3] mainly due to the fact that the tools used for this purpose are not adapted to the assessment of subtle abnormalities, e.g. related to the functioning of the prefrontal cortex (e.g., responsible for executive functions) [1].

The results of studies carried out in developed countries indicate proper cognitive functioning in PHIV+ children treated with HAART (highly active antiretroviral therapy) and in PHEU (perinatally HIV-exposed but uninfected) children [2, 4–10].

However, some observations confirmed the presence of language [2, 11, 12] and memory deficits, as well as executive functions deficits [2, 8, 9, 13–16] in PHIV+ children treated with HAART with medications that penetrate the blood-brain barrier. The most commonly described deficits of executive functioning include sequencing and planning [5, 8], response inhibition [8], working memory [5, 6, 8, 13–17] (including visuospatial working memory, VMW [2, 5]), flexibility of attention [2], simple response time [2], and processing speed [2, 6, 13, 15, 18].

Importantly, executive functions deficits in PHIV+ children with no symptoms of neuroinfection were found to be independent of infection stage [2, 8]. Some authors claim that the presence of executive functions deficits applies to all PHIV+ children and that they serve as early markers of the CNS HIV infection, despite the absence of clinical symptoms, found in most of the respondents. This seems to be a consequence of the implementation of HAART therapy, owing to which encephalopathy (diagnosed according to the Centers for Disease Control and Prevention [19] definition) ceases to be the expected consequence of HIV neuroinfection, and executive function disorders become such a consequence [2, 6, 8, 18].

Cognitive functioning is primarily affected by the infection's course. Performance on tests of cognitive functions in children and adolescents with AIDS (acquired immune deficiency syndrome) acquired before the age of five is much worse despite improvement in clinical status later in life [7, 14, 18, 20]. Problems regarding memory and visuospatial functions were most often observed in these groups [8] as opposed to children with no class C infection, who had normal results, similar to HIV-exposed but uninfected children (PHEU) [7].

The results of a study by Koekkoek et al. [2] testing possible relationships between infection-related clinical factors and executive function deficits showed better results regarding attention and working memory domains for children with higher CD4 lymphocytes level at the beginning of treatment and longer ARV (antiretroviral) treatment time. The results of other studies have confirmed that high viral load and low CD4 lymphocytes level are predictors of neurocognitive disorders. This has been explained by worse CNS renewal potential compared to other systems but also less effectiveness of HAART treatment in the CNS domain [6, 12, 14, 18, 21, 22]. Although the consequences of ARV therapy on the developing brain are yet to be fully recognized, the current guidelines recommend starting ARV therapy right after diagnosis of the infection [23, 24]. It seems that early introduction of treatment that has a positive impact on a child's immunological status may be beneficial for cognitive development [25]; however, not all studies have confirmed this observation [12, 26].

The expression of cognitive impairments in PHIV+ children is also influenced by environmental factors [6, 14, 27, 28], yet their interaction with clinical factors is not entirely clear. Llorente et al. [29], analyzing the cognitive functioning of PHIV + children, showed that the differences ceased to be significant after taking into account the influence of many environmental factors (such as race, maternal education, family income, prematurity, low birth weight, alcohol and drug use during pregnancy). The formulation of ultimate conclusions about the cognitive functioning of PHIV+ children is limited by the small number of studies, group heterogeneity and the diversity of assessed cognitive functions, which justifies further research.

This study aimed to assess the presence of cognitive impairments in children and adolescents with vertically transmitted HIV infection and to determine possible relationships with clinical and sociodemographic variables.

Material

The study group included 50 patients with perinatal HIV infection, aged 6–18 yyears, from the Department of Children's Infectious Diseases at the Medical University of Warsaw. The exclusion criteria included other routes of HIV infection, the presence of a chronic somatic condition other than HIV infection, the presence of any problem that could limit cooperation (inability to communicate in the Polish language), and the lack of child or caregiver consent. Two age – and sex-matched control groups were formed. The first reference group consisted of 24 healthy children and adolescents with HIV-infected mothers (perinatally HIV-exposed but uninfected; PHEU), who were recruited as ex-patients of the Department of Children's Infectious Diseases at the Medical University of Warsaw and clients of non-governmental organizations helping people infected with HIV. The second reference group consisted of 43 healthy children and adolescents with uninfected parents or without a history of HIV infection

in family members (HIV-non-Affected; HIV-nA), who were recruited through social networking websites and in Warsaw schools.

Methods

CANTAB Research Suite (Cambridge Neuropsychological Test Automated Battery; CANTAB) [30] was used in the assessment of cognitive functions. CANTAB is language-independent, culturally neutral, non-invasive, and require no technical knowledge or prior familiarity with computers. The CANTAB battery has never been used before in studies with children and adolescents with HIV infection (it was used in HIV-infected adults). However, it is a tool commonly used in other pediatric populations (e.g., in studies in children with ADHD).

Due to the lack of other studies on the Polish population and small samples, no comparisons with population norms were made in the current study. Untransformed scores were used in the statistical analyses.

The following tests were used:

1. MOT (Motor Screening Tasks), to introduce the study procedure. Its outcome measures include (1) the latency – speed of response between the presentation of the stimuli and the response; and (2) the mean error – which refers to the accuracy of touch, measured as a distance between the touch point and the centers of the stimuli.
2. RTI (Reaction Time) – an attention test that provides an assessment of reaction time in response to visual stimuli located in either a predictable position (simple reaction time) or a random position (choice reaction time). The outcome measures include (1) simple/five-choice reaction time – the reaction time between the presentation of a stimulus in a defined or random position; and (2) simple/five-choice movement time, the movement time in response to the presentation of the stimuli in defined or random positions.
3. SOC (Stockings of Cambridge) – a spatial planning and working memory test. The outcome measures include the following: (1) problems solved in minimum moves; (2) mean moves for 2-, 3-, 4 – and 5-move problems; (3) initial thinking time for 2-, 3-, 4 – and 5-move problems – the time needed to initiate the response (the time difference between independent task-solving module and the solution-copying module), interpreted as a measure of time needed for solution planning; and (4) subsequent thinking time for 2-, 3-, 4 – and 5-move problems.
4. IED (Intra-Extra Dimensional Set Shift) – a test of shifting attention. Its outcome measures include the following: (1) stages completed; (2) completed stage errors – the number of errors in each stage; (3) pre-ED Errors – the number of errors made before extra-dimensional shift test; (4) EDS errors – errors made during extra-dimensional shift change; (5) total errors (adjusted) – the chance for error is

smaller in cases when the task is not completed; in such a case, 25 errors are added to make comparisons with participants who completed the task; and (6) total trials (adjusted) – the number of deals for each level completed; with 50 deals added for each uncompleted level. Additionally, some analyses use parameters from level 9 (errors, latency, trials) as a measure of extradimensional reversal learning.

5. SWM (Spatial Working Memory) – a measure of the ability to update, refresh, and maintain spatial location information and maintain this data in working memory. The outcome measures include (1) between error – defined as selecting boxes that have already been found to contain a token in the ongoing task; and (2) strategy – the assessment of strategy based on the number of new box-scanning sequences on the most difficult level (six and eight boxes), with a high score (multiple sequences starting with different squares) reflecting weak strategy use.

During the initial interview, using an original survey filled in by a legal guardian, we collected basic information about the participant and the family, as well as information about environmental and sociodemographic factors. Participation in the study was voluntary. Informed consent forms were signed by both a child and a legal guardian prior to the study. The study was approved by the Ethics Committee of Medical University of Warsaw (approval no: KB 4/2012).

Descriptive statistics include medians and interquartile ranges (IQR). Due to the limited sample size and significant differences in this aspect between the compared groups, as well as the strong skewness of a number of outcome measures and the presence of outliers, the Mann-Whitney U test was used for all intergroup comparisons for continuous variables. Relationships between continuous variables were assessed using the non-parametric Spearman's *rho* correlation coefficient. The Chi-square or Fisher's exact test were used to assess the significance of differences in the distributions of dichotomous variables. p-values below 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

The PHIV+ group consisted of 50 patients. The PHEU group consisted of 24 subjects, whereas the HIV-nA group included 43 participants. Significant differences in intergroup comparisons (PHIV+ *vs.* PHEU and PHIV+ *vs*. HIV-nA) were found for some demographic parameters (Table 1).

Table 1. **Demographics of PHIV+, PHEU and HIV-nA groups and results of intergroup comparisons (PHIV+ vs. PHEU and PHIV+ *vs.* HIV-nA)**

	PHIV+ (n = 50)	PHEU (n = 24)	HIV-nA (n = 43)	PHIV+ vs. PHEU	PHIV+ vs. HIV-nA	PHEU vs. HIV-nA
	n (%)	n (%)	n (%)	p	p	p
Boys	25 (50)	11 (45.8)	22 (51.2)	0.930	1	1
Girls	25 (50)	13 (54.2)	21 (48.8)			
Resides with:						
Biological parent	33 (66)	18 (75.0)	43 (100.0)			
Adoption/foster family	10 (20)	5 (20.8)	0 (0.0)	0.606	<0.001	0.001**
No data	7 (14)	1 (4.2)	0 (0.0)			
Full family	28 (56)	20 (83.3)	32 (74.4)	0.079	0.204	0.593
No data	3 (6)	0 (0.0)	0 (0.0)			
Delivery:						
In term	23 (46)	15 (62.5)	33 (76.7)			
Pre-term or post-term	12 (24)	7 (29.2)	8 (18.6)	1	0.231	0.433
No data	15 (30)	2 (8.3)	2 (4.6)			
Stressful life events of a child	23 (46)	15 (62.5)	21 (48.8)	1	0.531	0.473
No data	14 (28)	1 (4.2)	2 (4.6)			
Education level of mothers:						
Primary or vocational	12 (24)	5 (20.8)	0 (0.0)			
Secondary or higher education	27 (54)	18 (75.0)	40 (93.0)	0.634	<0.001	0.004**
No data	11 (22)	1 (4.2)	3 (7.0)			
Mother's contacts with psychiatrist/psychologist	18 (36)	13 (54.2)	17 (39.5)	0.536	0.922	0.369
No data	10 (20)	1 (4.2)	2 (4.6)			
Education level of fathers:						
Primary or vocational	14 (28)	6 (25.0)	0 (0.0)			
Secondary or higher education	16 (32)	14 (58.3)	34 (79.1)	0.376	<0.001	0.001**
No data	20 (40)	4 (16.7)	9 (20.9)			
Father's contacts with psychiatrist/psychologist	11 (22)	6 (25.0)	3 (7.0)	0.788	0.016	0.066**
No data	11 (22)	4 (16.7)	10 (23.0)			

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	Med	IQR*	Med	IQR*	Med	IQR*	p	p	p
Age – median (months)	156.5	88.5	97.5	59.6	143.0	71.0	0.005	0.071	0.131
SES***	6	2.5	5	1.50	7	1.00	0.33	0.003	<0.001

* interquartile range

** Fisher's exact test

***Socioeconomic status

The clinical characteristics of the PHIV+ group are presented in Table 2 and 3. Data on HIV infection were collected from the parents. The presence of missing data stems from the fact that not all parents provided us with information on the matter.

Table 2. **Clinical characteristics of the PHIV+ group. Part 1**

	n (%)		
Awareness of HIV infection	29 (58)		
Smoking during pregnancy	12 (24)		
Substance use in pregnancy	7 (14)	HIV encephalopathy in a child	n (%)
Alcohol consumption in pregnancy	3 (6)		9 (18)
HCV infection in children	7 (14)		
HIV diagnosis before pregnancy	4 (8)		
Current (at the time of the study) HIV category according to CDC:	n (%)	Ultimate HIV category according to CDC:	n (%)
– N	40 (80)	– A	20 (40)
– A	5 (10)	– B	17 (34)
– B	0 (0)	– C	13 (26)
– C	5 (10)		
Current (at the time of the study) HIV immunologic status according to CDC:	n (%)	Ultimate HIV immunologic status according to CDC:	n (%)
– 1	47 (94)	– 1	13 (26)
– 2	3 (6)	– 2	18 (36)
– 3	0 (0)	– 3	20 (40)
ARV treatment initiation:	n (%)	ARV treatment at the time of the study:	n (%)
– before the age of 3 months,	7 (14)	– children on medication	48 (96)
– before the age of 12 months	23 (46)	– children without medication	2 (4)
– never treated	1 (2)		
– No data	1 (2)		

CDC – Centers for Disease Control and Prevention; ARV – antiretroviral

Table 3. **Clinical characteristics of the PHIV+ group. Part 2**

	On diagnosis	On treatment initiation	At the time of the study
Viremia; Copies of HIV RNA/ml:	n (%)	n (%)	n (%)
>100,000	25 (50)	24 (48)	0 (0)
10,000–100,000	14 (28)	16 (32)	3 (6)
401–10,000	0 (0)	2 (4)	1 (2)
<400	1 (2)	1 (2)	46 (92)
No data	10 (20)	7 (14)	0 (0)
Log10; Copies of HIV RNA/ml:			
>5 log10	20 (40)	10 (20)	
3–5 log10	12 (24)	18 (36)	No data
<3 log10	2 (4)	2 (4)	
No data	16 (32)	10 (20)	
% of CD4 lymphocytes			
0–14%	12 (24)	11 (22)	12 (24)
15–24%	12 (24)	13 (26)	16 (32)
≥25%	24 (48)	23 (46)	22 (44)
No data	2 (4)	3 (6)	0 (0)
CD4 lymphocytes n/l:			
0–199	7 (14)	7 (14)	0 (0,0)
200–499	9 (18)	9 (18)	3 (6)
500–749	2 (4)	4 (8)	11 (22)
750–999	5 (10)	5 (10)	17 (34)
>1000	25 (50)	23 (46)	19 (38)
No data	2 (4)	2 (4)	0 (0)
Detectable viremia at the time of the study	-	-	5 (10)

CANTAB

Further analyses were performed for the whole sample, as well as separately for the 6–11 and 12–18 age groups. The decision was motivated by the wide age range in the experimental and reference groups and significant differences in median age between the PHIV+ and PHEU groups. Data were obtained for n = 50 people from the PHIV+ group, n = 24 from the PHEU group and n = 43 from the HIV-nA group. The CANTAB test results and intergroup comparisons are presented in Table 4. Significant group differences were found both in the analysis for the whole sample and in the 12–18 year-old subgroup.

Table 4. **The comparison of CANTAB median scores: PHIV+ *vs.* PHEU and PHIV+ *vs.* HIV-nA (Mann Whitney U Test); age group 6–18 years and 12–18 years**

CANTAB	PHIV+		PHEU		HIV-nA		PHIV+ vs. PHEU	PHIV+ vs. HIV-nA
	Med	IQR	Med	IQR	Med	IQR	p	p
6–18 years	n = 50		n = 24		n = 43			
RTI								
Mean simple movement time*	355.4	153.1	346.6	53.0	319.0	97.4	0.804	0.007
Mean five choice movement time*	360.7	119.6	385.4	113.8	319.4	93.7	0.575	0.004
SOC								
Mean initial thinking time 4 moves	2782.0	2520.0	1954.0	1645.0	2634.0	2256.0	0.032	0.858
Mean initial thinking time 5 moves	3558.0	3311.0	2344.0	2640.0	2712.0	4624.0	0.009	0.450
Mean subsequent thinking time 2 moves	0.0	0.0	0.0	140.1	0.0	0.0	0.030	0.890
IED								
Completed stage errors	13.0	10.0	24.0	12.3	14.0	12.5	0.006	0.478
Pre-ED errors	6.0	2.0	7.0	1.3	5.0	3.5	0.040	0.044
SWM								
Between errors	34.5	31.3	45.5	32.5	22.0	26.0	0.130	0.009
12–18 years	n = 26		n = 6		n = 21			
MOT								
Mean error	11.5	4.6	11.3	2.9	14.1	2.9	0.869	0.018
RTI								
Mean five choice movement time*	355.7	87.4	329.1	42.5	319.4	92.9	0.331	0.022
SOC								
Mean moves 5 moves	7.5	1.7	6.4	1.5	6.8	1.5	0.073	0.019
Mean subsequent thinking time 4 moves	332.2	1456.2	0.0	0.0	554.0	1089.8	0.009	1.000
IED								
Pre-ED errors	6.5	1.8	7.0	0.8	5.0	2.0	0.691	0.015
SWM								
Between errors	28.0	23.8	14.5	18.8	11.0	12.0	0.140	0.007

*Latency/Time – [ms]

Clinical and sociodemographic factors

Due to the small subgroup sizes, analyses of relationships between the CANTAB results and the clinical and sociodemographic factors were carried out on a 6–18 year-old group. Significant differences in CANTAB results were found in groups differentiated by sex, awareness of diagnosis and ARV treatment initiation (Table 5).

Table 5. **Significant differences in CANTAB scores in subgroups devised by sociodemographic and clinical factors: PHIV+ group**

CANTAB	Med	IQR	Med	IQR	p
	Girls (n = 25)		Boys (n = 25)		
MOT					
Mean error	11.6	3.8	13.5	4.3	0.009
RTI					
Median simple movement time*	374.5	128.0	312.5	142.0	0.023
	No awareness of HIV infection (n = 21)		Awareness of HIV infection (n = 29)		
MOT					
Mean latency*					
RTI					
Mean simple reaction time*	785.6	134.6	660.1	143.8	0.009
Mean five choice reaction time*	385.2	178.0	292.4	56.4	0.001
SOC	397.2	100.5	325.3	56.6	0.006
Problems solved in minimum moves	6.0	2.0	8.0	2.0	0.007
Mean subsequent thinking time 2 moves	0.0	79.4	0.0	0.0	0.010
Mean subsequent thinking time 3 moves	426.0	1565.0	0.0	0.0	0.002
IED	8.5	2.0	9.0	0.0	0.015
Stages completed	14.5	18.8	7.0	10.0	0.014
ED errors	42.5	32.0	16.0	10.0	0.002
Total errors adjusted	131.0	51.5	76.0	15.0	0.002
Total trials adjusted	47.0	19.0	28.0	23.0	0.001
SWM					
Between errors					
	ARV treatment before the age of 3 months (n = 7)		ARV treatment after the age of 3 months (n = 40)		
IED					
Stages completed	7.0	1.5	9.0	0.0	0.017
Total errors adjusted	56.0	26.5	18.5	21.5	0.025
Total trials adjusted	150.0	27.0	82.5	45.3	0.031

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	ARV treatment before the age of 12 months (n = 23)		ARV treatment after the age of 12 months (n = 24)		
MOT					
Mean error					
SOC	13.7	4.1	11.6	4.6	0.016
Mean subsequent think time 2 moves	0.0	18.6	0.0	0.0	0.009
Mean subsequent think time 3 moves	348.3	859.9	0.0	0.0	0.001
Mean subsequent think time 4 moves	1183.0	1411.7	239.1	980.7	0.026
IED	9.0	2.0	9.0	0.0	0.038
Stages completed	10.0	6.5	15.5	9.5	0.025
Completed stage errors					

*Latency/Time – [ms]

The following statistically significant relationships were found between the results obtained in the CANTAB tests and the child's age at the time of the study: MOT mean latency (*rho* = – 0.39; $p = 0.005$); RTI mean simple reaction time (*rho* = – 0.57; $p < 0.001$); mean five-choice reaction time (*rho* = – 0.61; $p < 0.001$); SOC problems solved in minimum moves (*rho* = 0.43; $p = 0.002$); mean initial thinking time-5 moves (*rho* = 0.35; $p = 0.013$); mean subsequent thinking time-2 moves (*rho* = – 0.43; $p = 0.002$); – 3 moves (*rho* = – 0.61; $p < 0.001$); – 4 moves (*rho* = – 0.29; $p = 0.045$), IED stages completed (*rho* = 0.39; $p = 0.006$); total errors adjusted (*rho* = – 0.43; $p = 0.002$); total trials adjusted (*rho* = – 0.43; $p = 0.002$), SWM strategy (*rho* = – 0.29; $p = 0.039$) and between errors (*rho* = – 0.45; $p = 0.001$).

We also found correlations for clinical factors:

(1) Viral load (Log10) on ARV treatment initiation and RTI mean five choice reaction time (*rho* = 0.34; $p = 0.026$); mean simple movement time (*rho* = 0.35; $p = 0.023$); SOC mean moves-2 moves (*rho* = 0.37; $p = 0.017$); mean subsequent thinking time-3 moves (*rho* = 0.32; $p = 0.041$), IED stages completed (*rho* = – 0.35; $p = 0.024$), ED errors (*rho* = 0.43; $p = 0.005$); total errors adjusted (*rho*=0.38; $p = 0.012$) and total trials adjusted (*rho* = 0.38; $p = 0.012$);

(2) CD4n/l on diagnosis and MOT mean error (*rho* = 0.60; $p < 0.001$), IED errors block 9/total errors stage 9/total latency stage 9 (*rho* = – 0.32; $p = 0.029$) and total trials stage 9 (*rho* = – 0.33; $p = 0.022$);

(3) CD4% on diagnosis and MOT mean error (*rho* = 0.52; $p < 0.001$), IED completed stage errors (*rho* = – 0.30; $p = 0.038$) and total latency stage 9 (*rho* = – 0.30; $p = 0.040$);

(4) CD4n/l on ARV treatment initiation and MOT mean error (*rho* = 0.65; $p < 0.001$), IED errors block 9/total errors stage 9 (*rho* = – 0.34; $p = 0.018$); total latency stage 9 (*rho* = – 0.35; $p = 0.017$) and total trials stage 9 (*rho* = – 0.36; $p = 0.012$);

(5) CD4% on ARV treatment initiation and MOT mean error (*rho* = 0.59; $p < 0.001$); IED completed stage errors (*rho* = – 0.30; $p = 0.040$); errors block 9/total errors stage 9 (*rho* = – 0.33; $p = 0.023$); total latency stage 9 (*rho* = – 0.34; $p = 0.021$) and total trials stage 9 (*rho* = – 0.34; $p = 0.019$);
(6) CD4n/l at the time of the study and IED stages completed (*rho* = – 0.32; $p = 0.024$); errors block 9/total errors stage 9 (*rho* = – 0.38; $p = 0.007$) and total latency stage 9/Total trials stage 9 (*rho* = – 0.39; $p = 0.006$).

Discussion

Our study was the first in Poland to evaluate the majority of members of the HIV-infected population aged 6–18 years. The CANTAB results were analyzed for two domains: (1) information processing speed (MOT and RTI tests); and (2) executive functions including working memory, visuospatial memory, planning, control, cognitive flexibility, abstract reasoning, reversal learning, goal-directed activity, and modulation of impulsive reactions (IED, SOC, SWM tests).

Impairments in cognitive functioning were found in all tests in the PHIV+ group: the results were significantly worse for working memory and movement initiation time compared with the HIV-nA group, as well as longer in-task planning time in comparison with the PHEU group. In comparison with both the HIV-nA and PHEU groups, the PHIV+ group had significantly worse results in attentional switching, cognitive flexibility and reversal learning. The results in the group aged 12–18 years indicated worse speed processing and executive functioning in the PHIV+ group in comparison with the HIV-nA group, in all tests. As executive functions develop and mature with age [31], it is therefore important to emphasize the results obtained by adolescents. This issue is also pointed out by Nichols et al. [14, 32] and Hunter et al. [14, 32], who emphasize that executive function disorders are especially visible in adolescence, hence the correct results obtained in younger age groups cannot be interpreted without reservations as evidence of the absence of cognitive deficits. Our observations are in line with the results of a study conducted by Cohen et al. [13], where lower processing speed was observed in PHIV+ children over 12 years of age in comparison with healthy subjects.

The negative impact of HIV infection on processing speed may be observed irrespective of the patient's immunological condition [2, 14, 32]. This is linked with the occurrence of HIV encephalopathy as well as the time-point at which the lowest level of CD4 lymphocytes coincided with the highest viral load. Worse cognitive functioning of adolescents from our experimental group in comparison with healthy subjects suggests that infection duration adversely affects executive functions. On the other hand, the conclusion can be drawn that, despite the negative influence of HIV, there was a developmental potential in patients with congenital infection (as evidenced by the positive correlation between age and CANTAB results in our

sample), such that the quality of performance in cognitive tests was better in older participants.

The results of the current study did not confirm significant differences between children diagnosed and undiagnosed with encephalopathy observed in other studies [5, 9, 14]. Additionally, no significant differences or relationships were found according to HIV clinical class, including class C. The observation is not in line with the findings of other authors who reported cognitive deficits in children with AIDS, irrespective of improved health condition [7, 8, 14, 18, 20, 22, 34].

Contrary to other studies [25], no definite protective role of early (before the age of 3 or 12 months) ARV treatment initiation was observed in the current results with regard to cognitive functions. Our results showed worse reversal learning, attention shifting and cognitive flexibility in children provided with ARV treatment before three months of age in comparison with a group who initiated treatment after that time. We assume that it could have been a group of children whose early treatment was due to the rapid expression of HIV symptoms immediately after delivery (or symptoms observed in pregnant mothers), which suggests greater severity of infection and, thus, a more negative effect on the development of the CNS. Furthermore, an analysis of the relationships between CANTAB test results and clinical factors showed that higher viral load values at ARV treatment initiation correlated with slower information processing, weaker planning, reversal learning, and cognitive flexibility. In view of the foregoing, it can be concluded that cognitive functioning is influenced not only by the current health condition but also the course of HIV infection. Similarly, Koekkoek et al. [2] emphasized the importance of the child's immunological condition before initiating ARV treatment and its duration as variables which determined the quality of, among others, working memory functioning. Observations suggest the decrease in CNS regeneration potential, despite successful ARV treatment [6, 12, 14, 18, 21]. On the other hand, Martin et al. [5] demonstrated that processing speed is better in children in better actual immunological condition.

The results of studies on sex-related speed processing are inconclusive – some results suggest higher processing speed in younger girls [35] and some in boys. Significant sex differences are observed in adolescence [31]. In our study, girls from the PHIV+ experimental group had worse movement times, which influenced processing speed in the RTI test. However, no negative impact on other cognitive tests was observed.

There are several important limitations of the study. The first is the lack of selection of control groups according to socio-economic status, which should be accounted for in the context of observations of Cohen et al. [13]. Other limitations which precluded extending the analyses beyond one-factor relationships was the small size of experimental and reference groups. Because more complex analyses could not be performed, the current study should be regarded as descriptive. The size and age of the

PHEU group, which was significantly younger than the experimental group, is another important limitation. Furthermore, the mothers of children who were exposed to the infection received ARV treatment when pregnant, which raises questions about the influence of this procedure on future cognitive functioning. Moreover, the CANTAB test battery has never before been used in the assessment of children and adolescents with congenital HIV infection. The tools are also not commonly used in Poland, which limits comparisons to the results of other studies or norms. An unsuccessful attempt (related to the sample size and sex distribution) was made to compare the results to population norms delivered by CANTAB software. For the above reasons, only intergroup comparisons were performed. Comorbid HCV infection diagnosed in seven children in the experimental group was a potential factor that could have influenced the cognitive functioning.

Conclusions

1. The cognitive functioning of adolescents with vertically transmitted HIV infection was worse compared to healthy subjects with uninfected parents.
2. A more severe course of HIV infection and its severity before starting treatment is associated with a greater severity of deficits in executive functions.

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References

1. Smith R, Wilkins M. *Perinatally acquired HIV infection: long-term neuropsychological consequences and challenges ahead*. Child Neuropsychol. 2015; 21(2): 234–268.
2. Koekkoek S, de Sonneville LM, Wolfs TF, Licht R, Geelen S. *Neurocognitive function profile in HIV-infected school-age children*. Eur. J. Paediatr. Neurol. 2008; 12(4): 290–297.
3. Phillips NJ, Hoare J, Stein DJ, Myer L, Zar HJ, Thomas K. *HIV-associated cognitive disorders in perinatally infected children and adolescents: a novel composite cognitive domains score*. AIDS Care. 2018; 30(sup1): 8–16.
4. Nozyce ML, Lee SS, Wiznia A, Nachman S, Mofenson LM, Smith ME et al. *A behavioral and cognitive profile of clinically stable HIV-infected children*. Pediatrics. 2006; 117(3): 763–770.
5. Martin SC, Wolters PL, Toledo-Tamula MA, Zeichner SL, Hazra R, Civitello L. *Cognitive functioning in school-aged children with vertically acquired HIV infection being treated with highly active antiretroviral therapy (HAART)*. Dev. Neuropsychol. 2006; 30(2): 633–657.
6. Smith R, Chernoff M, Williams PL, Malee KM, Sirois PA, Kammerer B et al. *Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence*. Pediatr. Infect. Dis. J. 2012; 31(6): 592–598.

7. Smith R, Malee K, Leighty R, Brouwers P, Mellins C, Hittelman J et al. *Effects of perinatal HIV infection and associated risk factors on cognitive development among young children*. Pediatrics. 2006; 117(3): 851–862.

8. Bisiacchi PS, Suppiej A, Laverda A. *Neuropsychological evaluation of neurologically asymptomatic HIV-infected children*. Brain Cogn. 2000; 43(1–3): 49–52.

9. Blanchette N, Smith ML, King S, Fernandes-Penney A, Read S et al. *Cognitive development in school-age children with vertically transmitted HIV infection*. Dev. Neuropsychol. 2002; 21(3): 223–241.

10. Thomaidis L, Bertou G, Critselis E, Spoulou V, Kafetzis DA, Theodoridou M. *Cognitive and psychosocial development of HIV pediatric patients receiving highly active anti-retroviral therapy: a case-control study*. BMC Pediatr. 2010; 10: 99.

11. Brackis-Cott E, Kang E, Dolezal C, Abrams EJ, Mellins CA. *The impact of perinatal HIV infection on older school-aged children's and adolescents' receptive language and word recognition skills*. AIDS Patient Care STDS. 2009; 23(6): 415–421.

12. Jeremy RJ, Kim S, Nozyce M, Nachman S, McIntosh K, Pelton SI et al. *Neuropsychological functioning and viral load in stable antiretroviral therapy-experienced HIV-infected children*. Pediatrics. 2005; 115(2): 380–387.

13. Cohen S, Ter Stege JA, Geurtsen GJ, Scherpbier HJ, Kuijpers TW, Reiss P et al. *Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls*. Clin. Infect. Dis. 2015; 60(7): 1111–1119.

14. Nichols SL, Brummel SS, Smith RA, Garvie PA, Hunter SJ, Malee KM et al. *Executive Functioning in Children and Adolescents With Perinatal HIV Infection*. Pediatr. Infect. Dis. J. 2015; 34(9): 969–975.

15. Phillips N, Amos T, Kuo C, Hoare J, Ipser J, Thomas KGF et al. *HIV-Associated Cognitive Impairment in Perinatally Infected Children: A Meta-analysis*. Pediatrics. 2016; 138(5): e20160893.

16. Robbins RN, Zimmerman R, Korich R, et al. *Longitudinal trajectories of neurocognitive test performance among individuals with perinatal HIV-infection and – exposure: adolescence through young adulthood*. AIDS Care. 2020; 32(1): 21-29.

17. Elliott-DeSorbo DK, Martin S, Wolters PL. *Stressful life events and their relationship to psychological and medical functioning in children and adolescents with HIV infection*. J. Acquir. Immune. Defic. Syndr. 2009; 52(3): 364–370.

18. Nachman S, Chernoff M, Williams P, Hodge J, Heston J, Gadow KD. *Human immunodeficiency virus disease severity, psychiatric symptoms, and functional outcomes in perinatally infected youth*. Arch. Pediatr. Adolesc. Med. 2012; 166(6): 528–535.

19. Centers for Disease Control and Prevention. *1994 revised classification system for Human Immunodeficiency Virus infection in children less than 13 years of age*. MMWR, 1994; 43(RR12): 1–10.

20. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. *The impact of AIDS diagnoses on long-term neurocognitive and psychiatric outcomes of surviving adolescents with perinatally acquired HIV*. AIDS. 2009; 23(14): 1859–1865.

21. Shanbhag MC, Rutstein RM, Zaoutis T, Zhao H, Chao D, Radcliffe J. *Neurocognitive functioning in pediatric human immunodeficiency virus infection: effects of combined therapy*. Arch. Pediatr. Adolesc. Med. 2005; 159(7): 651–656.

22. Malee KM, Chernoff MC, Sirois PA, Williams PL, Garvie PA, Kammerer BL. *Impact of Perinatally Acquired HIV Disease Upon Longitudinal Changes in Memory and Executive Functioning*. J. Acquir. Immune Defic. Syndr. 2017; 75(4): 455–464.

23. Foster C, Bamford A, Turkova A, Welch S, Klein N; P*ENTA Guidelines Writing Group and PENTA steering committee. Paediatric European Network for Treatment of AIDS Treatment Guideline 2016 update: antiretroviral therapy recommended for all children living with HIV.* HIV Med. 2017 Feb;18(2):133-134. doi: 10.1111/hiv.12399.

24. *Guidelines for the use of antiretroviral agents in pediatric HIV infection 2016* [updated March, 1, 2016. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. (retrieved 12.12. 2016).

25. Laughton B, Cornell M, Boivin M, Van Rie A. *Neurodevelopment in perinatally HIV-infected children: a concern for adolescence*. J. Int. AIDS Soc. 2013; 16: 18603.

26. Puthanakit T, Ananworanich J, Vonthanak S, Kosalaraksa P, Hansudewechakul R, van der Lugtet J et al. *Cognitive function and neurodevelopmental outcomes in HIV-infected Children older than 1 year of age randomized to early versus deferred antiretroviral therapy: the PREDICT neurodevelopmental study*. Pediatr. Infect. Dis. J. 2013; 32(5): 501–508.

27. Sherr L, Croome N, Parra Castaneda K, Bradshaw K, Romero RH. *Developmental challenges in HIV infected children – An updated systematic review*. Children and Youth Services Review. 2014; 45: 74–89.

28. Coscia JM, Christensen BK, Henry RR, Wallston K, Radcliffe J, Rutstein R. *Effects of home environment, socioeconomic status, and health status on cognitive functioning in children with HIV-1 infection*. J. Pediatr. Psychol. 2001; 26(6): 321–329.

29. Llorente AM, Brouwers P, Leighty R, Malee K, Smith R, Harris L et al. *An analysis of select emerging executive skills in perinatally HIV-1-infected children*. Appl. Neuropsychol. Child. 2014; 3(1): 10–25.

30. Sahakian BJ, Owen AM. *Computerized assessment in neuropsychiatry using CANTAB: discussion paper*. J. R. Soc. Med. 1992; 85(7): 399–402.

31. Gur RC, Richard J, Calkins ME, Chiavacci R, Hansen JA, Bilkeret WB et al. *Age group and sex differences in performance on a computerized neurocognitive battery in children age 8–21*. Neuropsychology. 2012; 26(2): 251–265.

32. Hunter SJ, Edidin JP, D. Hinkle C. *The developmental neuropsychology of executive functions*. In: Hunter SJ, Sparrow EP, editors. *Executive Function and Dysfunction: Identification, Assessment and Treatment*. Cambridge: Cambridge University Press; 2012. P. 17–36. doi: 10.1017/CBO9780511977954.004.

33. Nagarajan R, Sarma MK, Thomas MA, Chang L, Natha U, Wright M. *Neuropsychological function and cerebral metabolites in HIV-infected youth*. J. Neuroimmune Pharmacol. 2012; 7(4): 981–990.

34. Nichols SL, Chernoff MC, Malee KM, Sirois PA, Woods SP, Williams PL et al. *Executive Functioning in Children and Adolescents With Perinatal HIV Infection and Perinatal HIV Exposure*. J. Pediatric Infect. Dis. Soc. 2016; 5(suppl 1): 15–23.

35. Li C, Zhu N, Zeng L, Dang S, Zhou J, Kang Y et al. *Sex differences in the intellectual functioning of early school-aged children in rural China*. BMC Public Health. 2016; 16: 288.

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