Cytomegalovirus infection associated with lower IQ in adolescent patients with schizophrenia spectrum disorders: A preliminary report

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\textbf{ABSTRACT}

Cytomegalovirus (CMV) infection of immunocompetent hosts is usually inapparent, but typically results in a non-silent chronic latency which is considerably more active than previously considered. In adults with schizophrenia spectrum disorders, CMV latent infection has been associated with cognitive disturbance including lower intelligence quotient (IQ). We hypothesized that the same pattern will be present in adolescent patients with schizophrenia spectrum disorders (early-onset non-affective psychosis). We included 17 adolescents with schizophrenia spectrum disorders (10 patients with schizophrenia, one patient with schizoaffective disorder and six patients with psychosis not otherwise specified), mean age 16.7 years, females 71\% and CMV seropositivity 35\%. Current IQ was estimated with the Wechsler Abbreviated Scale of Intelligence. CMV immunoglobulin G (IgG) concentrations were measured by solid-phase immunoassays and expressed as dichotomous measures (seropositive/CMV$^+$ vs. seronegative/CMV$^-$). CMV$^+$ patients (mean IQ 91) had significantly lower full-scale IQ than CMV$^-$ patients (mean IQ 110) (20 units difference; $p = 0.001$). Post-hoc analyses showed that CMV$^+$ patients had both lower performance and lower verbal IQ relative to CMV$^-$ patients ($p = 0.001$ and 0.049, respectively). In this preliminary report, we found that CMV IgG seropositivity, reflecting previous CMV infection and current latency, was associated with lower IQ. This may be indicative of an unfavorable impact of CMV infection on general intelligence in early-onset non-affective psychosis.

\section{1. Introduction}

Human cytomegalovirus (CMV) is a common DNA beta-herpesvirus infecting hosts of all ages with a high universal seroprevalence. In immunocompetent individuals, the primary infection is typically asymptomatic or mild with mononucleosis-like symptoms, whereas infection of immunodeficient hosts as well as congenital infection can have detrimental impact (Dupont and Reeves, 2016). CMV is implicated in AIDS dementia (Goplen et al., 2001) while congenital CMV can have dramatic effects on the central nervous system including permanent neurological deficits and cognitive delay (Elliott, 2011). A primary CMV infection of immunocompetent individuals after birth results in chronic latency in cells of the hematopoietic system, with more recent research suggesting also brain cells, and can be complicated with subsequent reactivations (Dupont and Reeves, 2016). In our recent study of adults with schizophrenia spectrum disorders, we found that CMV infection was associated with lower intelligence quotient (IQ) in women (Andreou et al., 2021b). To our knowledge, this association has not been studied in adolescent patients. We hypothesized that in adolescent patients with schizophrenia spectrum disorders (non-affective early-onset psychosis with an age of onset <18 years), CMV immunoglobulin G (IgG) seropositivity, reflecting previous viral infection and current latency, will be associated with lower IQ, and that such a putative association may be sex-dependent.

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2. Methods

2.1. Participants

The Thematically Organized Psychosis study for Youth (Youth-TOP) is a thematic research effort on psychotic disorders and the study protocol for adolescence at the Norwegian Centre for Mental Disorders Research (NORMENT, Oslo, Norway; www.med.uio.no/norment/english). Inclusion criteria for the Youth-TOP participants were meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a psychotic disorder, age 12–18 years and being able to communicate in Norwegian. Exclusion criteria were previous moderate/severe head injury, IQ < 70 and neurological disorder or any medical illness that could affect brain function. Patients with substance use disorders (including alcohol use disorder) were also excluded. The patients were recruited from inpatient and outpatient units in Oslo, Norway. Medical doctors and psychologists assessed the patients with the Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997).

For the current study, participants were drawn from the Youth-TOP study cohort (2013–2014) if they had a schizophrenia spectrum disorder as well as CMV IgG and IQ data. The final sample consisted of 17 adolescent patients, mean age (standard deviation) 16.7 years (1), females 71%, CMV seropositivity 35%, with schizophrenia spectrum disorders, i.e. 10 patients with schizophrenia, one patient with schizoaffective disorder and six patients with psychosis not otherwise specified. The study was approved by the local ethics committee and the Norwegian Data Inspectorate and complies with the Helsinki Declaration of 1975, as revised in 2008. Written Informed consent was obtained from patients or their parents/guardians if the patient was younger than 16 years.

2.2. Measurements

Blood samples were drawn from all participants. CMV IgG antibody concentrations were measured and expressed as dichotomous measures (seropositive/CMV + vs. seronegative/CMV-) as previously described (Andreou et al., 2021b). We evaluated IQ using a licensed translated version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007). We assessed all participating patients with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and defined the age of onset as the age of the first emergence of psychotic symptoms. We assessed the current use (yes/no) of antipsychotic medication, and calculated the current chlorpromazine equivalent doses (CPZ) in mg/day as well as the lifetime CPZ (CPZ years) (Andreasen et al., 2010).

2.3. Statistics

In the bivariate analysis, we assessed differences between CMV- and CMV + patients in sex, age, years of education, maternal years of education (as a proxy of socioeconomic status), age of onset, duration of illness, PANSS total score, the current use of antipsychotics, current and lifetime CPZ, handedness, body mass index (BMI), heart rate, systolic and diastolic blood pressure. In the multivariate analysis (analysis of covariance; ANCOVA), we investigated main and interaction effects of CMV IgG status (CMV-/CMV-) and sex on IQ adjusting for age as well as variables that differentiated CMV- and CMV + patients in the bivariate analysis. Further, due to the small sample size, we conducted sensitivity analyses in order to confirm the results of the main multivariate analysis: a) Mann-Whitney U Test, b) median regression (a special case of quantile regression) and c) bootstrapping (1000 number of samples, seed 2,000,000). Finally, WASI consists of four subtests: the vocabulary and similarities subtests forming the verbal IQ, and the block design and matrix reasoning subtests forming the performance IQ. We conducted post-hoc age- and sex-adjusted ANCOVAs on verbal IQ and performance IQ.

The statistical analysis was conducted with IBM SPSS Statistics 28.

3. Results

3.1. Main analysis

The bivariate analysis showed that CMV- and CMV + patients did not significantly differ in any of the demographic or clinical variables (Table 1). In the initial multivariate model (full factorial ANCOVA), there was no statistically significant CMV IgG status-by-sex interaction on IQ whilst controlling for age, F(1, 12) = 0.376, p = 0.551. In the final ANCOVA without the interaction term, the effect of CMV IgG status on IQ was statistically significant, F(1,13) = 18.168, p < 0.001, whilst controlling for sex (p = 0.210) and age (p = 0.539). The estimated IQ means in CMV- and CMV + patients were 110.16 (95% CI, 104.57 to 115.75) and 90.71 (95% CI, 82.97 to 98.45), respectively (Fig. 1). In the final ANCOVA, there was homogeneity of variances (Levene’s test, p = 0.715). There were no studentized residuals greater than three standard deviations (range −1.76 to 2.62), while there was one studentized residual greater than 2.5 standard deviations. Excluding this case did not change the results still showing a significant inverse association between seropositivity and IQ (p = 0.001) whilst controlling for age and sex. The distribution of the residuals of the overall model (n = 17) as well as for CMV- (n = 11) and CMV+ (n = 6) groups separately did not deviate from normality assessed with Shapiro-Wilk test of normality (p = 0.623, Table 1)

| Table 1: Group differences between cytomegalovirus (CMV) immunoglobulin G (IgG) seronegative (CMV-) and seropositive (CMV+) adolescent patients with early-onset psychosis in sex, age, years of education, maternal years of education, age of onset, duration of illness, the Positive and Negative Syndrome Scale (PANSS) total score, the percentage of patients on antipsychotics as well as the chlorpromazine equivalent doses (CPZ) and the lifetime CPZ (CPZ years), handedness (right-handedness vs. left-handedness/ambidexterity), body mass index (BMI), resting heart rate, systolic and diastolic blood pressure. Two patients were on antidepressants. Due to the small sample size the associations were also tested with nonparametric statistics. |
|-----------------|-----------------|-----------------|
| CMV- Mean (SD) | CMV+ Mean (SD)  |
| Sex (females %) | 63.6 (8.3) | 63.6 (8.3) | 0.394 0.600 |
| Age (years)     | 16.5 (1.6) | 17.1 (0.6) | 0.278 0.462 |
| Education years | 9.7 (1) | 10.0 (0.7) | 0.596 0.743 |
| Education years mother | 15.6 (2) | 14.8 (0.8) | 0.367 0.180 |
| Age of onset    | 12.3 (4.2) | 12.5 (3) | 0.923 0.660 |
| Duration of illness | 2.3 (2.4) | 2.3 (2) | 0.933 0.808 |
| PANSS total score | 72.6 (16) | 76.2 (16.4) | 0.664 0.650 |
| Current use of antipsychotics (%) | 36.3 | 66.7 | 0.232 0.335 |
| Current CMV (mg/day) | 275.7 (308.6 (147) | 0.792 0.686 |
| Lifetime CPZ (%) | 16.2 (24.8) | 25.9 (15.9) | 0.513 0.352 |
| Handedness (right-handedness %) | 90.9 | 100 | – 1.000 |
| BMI (kg/m²) | 21.8 (5.6) | 24.5 (5.2) | 0.363 0.180 |
| Resting heart rate (beats per minute) | 72 (9.6) | 70.5 (9.9) | 0.794 0.949 |
| Systolic blood pressure (mmHg) | 113 (9.7) | 117 (10.1) | 0.497 0.661 |
| Diastolic blood pressure (mmHg) | 76.8 (9.6) | 72 (15) | 0.469 0.661 |

a Chi-square test or t-test.  
b Mann-Whitney U test or Fisher’s exact test.  
c Among patients currently on antipsychotics (n = 8).  
d Among non-antipsychotic-naive patients (n = 10).  
e One missing value.  
f Two missing values.
patients with schizophrenia spectrum disorders had significantly lower verbal and performance IQ than CMV- patients (p < 0.001). Both associations were confirmed with Mann-Whitney U tests (p = 0.718 and 0.867, respectively).

Further, although not statistically significant, more CMV+ patients were currently on antipsychotics than CMV- patients (Table 1), and further, CMV+ patients had higher lifetime CPZ than CMV- patients (Table 1). Adding these variables into the final model did not change any results; CMV+ patients had still significantly lower IQ than CMV- patients in both models (p = 0.001 and < 0.001, respectively).

3.2. Post-hoc WASI subtests analysis

In age- and sex-adjusted ANCOVAs, we found that CMV+ patients had lower verbal and performance IQ than CMV- patients (p = 0.049 and 0.001, respectively). Both associations were confirmed with Mann-Whitney U Tests (p = 0.040, 0.001).

4. Discussion

The main finding of the present study was that CMV+ adolescent patients with schizophrenia spectrum disorders had significantly lower IQ than CMV- patients (20 units difference) (Fig. 1). This was shown not only for full-scale IQ but also for performance and verbal IQ. Of note, CMV is never cleared by the host (Wills et al., 2015), and IgG seropositivity reflects thereby previous infection and current latency. Further, viral reactivations occur not only in immunocompromised hosts causing apparent illness, but also in immunocompetent hosts being typically asymptomatic (Forte et al., 2020). Our results are suggestive of a CMV-related disturbance in general intelligence among patients with schizophrenia spectrum disorders, but we still cannot determine if the lower IQ among CMV+ patients is related to the primary infection, the viral reactivations and/or the chronic infection.

The effect size was larger compared to previous studies in healthy adults, adults with psychotic disorders (Andreou et al., 2021b) and healthy children/adolescents (Tarter et al., 2014) indicating that adolescent patients with psychosis might be particularly susceptible to a negative impact of CMV infection. CMV has a major impact on progenitor/immature nerve cells while differentiated/mature cells are more resilient (Cheeran et al., 2009). Maturation aberrations in psychosis in the context of neurodevelopmental disturbances (Owen et al., 2011), and maturation processes during adolescence when the human brain is still under construction (Arain et al., 2013) may explain the higher vulnerability of adolescent patients. The observed vulnerability to CMV effects in psychosis may also be due to the suggested blood-brain barrier deficiency facilitating viral invasion, an inflammatory environment enhancing CMV reactivations, and immunological disturbances (Andreou et al., 2021b).

Cognitive disturbance is a key characteristic in psychotic disorders (Green et al., 2019), and our results suggest that CMV might be an important environmental factor. Cognitive abnormalities in psychosis may reflect underlying neurodevelopmental abnormalities (Melle, 2019), and are often present prior to the onset of the disorder (Ohi et al., 2017). An IQ decline after the onset of the psychotic symptoms is present in some but not all patients (Ohi et al., 2017), and this heterogeneity may reflect genetic and environmental influence, including pathogens. Of note, in psychosis, general intelligence represents an essential predictor of treatment response in evidenced-based psychological interventions (Seccomandi et al., 2021; Vita et al., 2021). In a recent analysis of data from 12 randomized control trials, it was shown that higher IQ at baseline was associated with larger cognitive improvement after cognitive remediation interventions (Seccomandi et al., 2021).

The congenital CMV infection is rather rare, and 0.2%–2% of newborns are born with CMV in different populations (Barlinn et al., 2018; Kawasaki et al., 2017). In stark contrast, the postnatal infection is very common, and CMV IgG seropositivity, reflecting CMV exposure, continuously increases during childhood, adolescence (Voigt et al., 2016) and adulthood (Lachmann et al., 2018). Of note, the CMV seroprevalence largely depends on geographic location and socioeconomic status (Cannon et al., 2010; Dupont and Reeves, 2016), with an estimated global seroprevalence of 83% in the general population being highest in Eastern Mediterranean and lowest in the European region (Zuhair et al., 2019). Large European epidemiological studies have shown a CMV seroprevalence of 22% at ages 1–2 years, 32% at ages 14–17 years (Voigt et al., 2016), and an overall CMV seroprevalence of 57% during adulthood (Lachmann et al., 2018). We recently reported a similar CMV IgG seropositivity in adult patients with schizophrenia spectrum disorders and healthy individuals, being 56% and 55%, respectively (Andreou et al., 2021b). In the current study, 35% (6/17) of the patients were CMV+, in accordance with the seropositivity previously found in healthy adolescents (Voigt et al., 2016). The high CMV seroprevalence in both the general population and in schizophrenia spectrum disorders means that the current results have potential relevance in terms of public health impact.

We have previously reported that CMV IgG seropositivity is linked to both cognitive and brain structural abnormalities among patients with schizophrenia spectrum disorders but not healthy individuals (Andreou et al., 2021a, 2021b) and we here show a CMV-related cognitive
disturbance already in adolescent psychosis. The present results, if replicated, can be suggestive of CMV preventive or therapeutic measures in adolescent patients with psychotic disorders and in children and adolescents with a high risk of developing psychosis. Despite ongoing promising research, to the best of our knowledge, there is to date no licenced CMV vaccine or licenced monoclonal antibody therapy (Struble et al., 2021). Susceptible individuals, including patients with psychosis or at risk of developing psychosis, could be a prioritized group when such options became available.

The present study has certain limitations. First, the number of patients was small, and the results are thus in need of replication. Further, as we did not include healthy controls, we cannot know if the observed association is restricted to patients. Interestingly, in our recent study among adults, there was no CMV-IQ association among healthy controls (Andreu et al., 2021b), but this needs to be studied in adolescence. Further, the study is cross-sectional and a causal relationship cannot be ascertained. Finally, we cannot know from the present results when the CMV + patients contracted the infection. However, we can conclude, based on the low percentage of the congenital CMV infection (Barlinn et al., 2018; Kawasaki et al., 2017) in stark contrast to the high percentage of CMV-infected participants in the studied group (35%), that the primary infection occurred for almost all or even all patients after birth diminishing the possibility that our finding reflects long-term cognitive impairment in congenitally infected hosts.

Summarizing, the results are indicative of a CMV-related cognitive disturbance in adolescent patients with schizophrenia spectrum disorders.

Author statement

TC and DA drafted the manuscript. DA performed the statistical analysis. TC and DA interpreted the data. DA supervised the study. RHY substantiated contributions to the interpretation of data, critically revised the manuscript for important intellectual content and approved the final version to be published.

Data availability

Data supporting the findings of the present study have repository at NORMENT/Oslo University Hospital. Restrictions apply to the availability of data and are thereby not publicly available. Data can be made available under reasonable request and with permission of NORMENT/ Oslo University Hospital, in accordance with the ethics agreements/research participants consent.

Conflicts of interest

OAA is a consultant to HealthLytix, and received speaker’s honorarium from Lundbeck and Sunovion. All other authors reported no potential conflicts of interest.

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