79. Children with COVID-19 Demonstrate Distinct Serum Cytokines Profiles According to Clinical Presentations

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Session: O-17. Hot Topics in Pediatric Viral and Fungal Infections

Background. Almost 4 million children have tested positive for Coronavirus Disease 2019 (COVID-19) as of June 3, 2021, representing 14% of all cases in USA. Children present with diverse clinical findings including the multisystem inflammatory syndrome in children (MIS-C). In this study, we measured serum cytokine concentrations in children with COVID-19 to identify differences in immune profiles according to clinical presentations.

Methods. A total of 133 children 0-21 years of age with COVID-19 were enrolled at Nationwide Children’s Hospital, Columbus, Ohio. Nasopharyngeal swab RT-PCR testing was used for SARS-CoV-2 detection and quantification. Clinical and laboratory information were obtained, and blood samples were collected for measurement of cytokines with a 92-plex inflammation assay (Olink). Normalized cytokine expression levels in patients were compared with serum samples from 66 pre-pandemic age-matched healthy controls.

Results. COVID-19 children included: 1) those identified by universal screening (n=47); 2) moderate disease (ward; n=48); 3) severe disease (PICU; n=20); 4) MIS-C (n=18). Children identified by universal screening were hospitalized for trauma, appendicitis or new onset diabetes among others. Children with symptomatic COVID-19 had significantly higher SARS-CoV-2 viral loads than children with MIS-C or those not hospitalized. Children with COVID-19, as well as those with MIS-C, showed inflammation via universal screening. Concentrations of interferon (IFN)-related cytokines (IFNg, CXCL9, CXCL10, CXCL11), interleukins (IL6, IL8, IL10, IL17A, IL18, IL24) and other inflammatory cytokines (TGF, TNF, VEGF, MCP, CD40) were significantly increased in children with acute COVID-19 and MIS-C compared with children identified by universal screening and healthy controls. These cytokines were positively correlated with C-reactive protein, D-dimer and disease severity in
COVID-19, but negatively correlated with viral loads (Fig 1). MIS-C showed stronger inflammatory response than acute COVID-19 (Fig 2).

**Figure 3. Correlation between cytokines and clinical variables**

Correlation of Age-adjusted cytokine expression values with viral load, disease severity, CRP and D-dimer. Pearson correlation coefficient is shown for each pair. Red: positive correlation; blue: negative correlation

Heatmap shows the differential expressed cytokines between MIS-C and acute severe COVID-19 (padj<0.05, FC>2). The age-adjusted expression values are normalized to the median of healthy controls. Red: up-regulation, blue: down-regulation.

**Conclusion.** We identified three cytokine clusters in children with COVID-19 according to clinical presentations. Correlations of serum cytokines with clinical/laboratory parameters could be used to identify potential biomarkers associated with disease severity in COVID-19.

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80. Heme Oxygenase-1 Gene promoter and associations with inflammation and subclinical vascular disease in Ugandan adolescents with and without HIV

**Background.** Heme oxygenase-1 (HO-1) is a cytoprotective enzyme with potent anti-inflammatory, and anti-oxidant effects. The HO-1 response is modulated by functional polymorphisms (a dinucleotide (GT)n repeat length variation) in the HO-1 gene promoter region which have been associated with cardiovascular disease (CVD) susceptibility in adults. HO-1 polymorphisms and their associations with markers of inflammation and CVD in Ugandan adolescents with (HIV+) and without HIV (HIV-) have not been investigated.

**Methods.** We included 177 children (92 HIV+, 85 HIV-) enrolled in an ongoing observational cohort study at the Joint Clinical Research Center, Kampala, Uganda. All HIV+ participants were on ART. HO-1 (GT)n allele genotypes were determined by PCR of the (GT)n repeat region followed by fragment size determination on a capillary sequencer in DNA extracted from blood samples. Allele designations were assigned by number of (GT)n repeats: S < 27, M 27-34, or L > 34 repeats.

**Results.** Median age (IQR) was 13 (11, 14), 44% were females, 86% had viral load < 20 copies/mL. 19% had a short allele genotype, 57% had a medium allele genotype and 44% had a long allele genotype (Figure). The shortest and longest allele length correlated with lower IMT in HIV- only (r=-0.36 and -0.30, respectively, p< 0.01 for both). Among biomarkers, only the medium allele correlated with oxidized lipids in HIV+ and with hsCRP and BIDG in HIV+ (p< 0.05). After adjusting for age, sex, and BMI, the presence of a long allele was associated with lower IMT. This was no longer significant after adjusting for markers of inflammation or oxidized lipids (Table).

**Heme Oxygenase-1 genotype allele length frequency in Ugandan cohort of HIV+ and HIV- youth**

| HO-1 (GT)n Allele Frequency (%) |
|---------------------------------|
| Total Cohort                    |
| LL     | ML     | MM    | SM    | SS    |
| 100    | 75     | 50    | 25    | 0     |

**Figure.** Heme Oxygenase-1 genotype allele length frequency in Ugandan cohort of HIV+ and HIV- youth. Allele length S= Short, M= Medium, L= Long. Allele designations were assigned by number of (GT)n repeats: S < 27, M 27-34, or L > 34 repeats.

**Table.** Associations with carotid intima-media thickness using quintile regression analysis for all participants

| Comparisons (GT)n allele length (S, M, L) | Odds Ratio (95% CI) |
|------------------------------------------|---------------------|
| S < 27 vs M 27-34                        | 0.74 (0.57-0.97)    |
| M 27-34 vs L > 34                        | 0.78 (0.61-0.99)    |

1: Models are adjusted for age (years), sex (male vs female), BMI (kg/m2) and HIV status (positive vs negative) 2: Models are adjusted for age (years), sex (male vs female), BMI (kg/m2), sCD14 (pg/mL) and HIV status (positive vs negative) 3: Models are adjusted for age (years), sex (male vs female), BMI (kg/m2), high sensitivity C reactive protein (mg/mL) and HIV status (positive vs negative) 4: Models are adjusted for age (years), sex (male vs female), BMI (kg/m2), oxidized lipids and HIV status (positive vs negative)

**Conclusion.** These findings underscore the potential of the HO pathways in modulating future risk for CVD in adolescents through inflammation. HIV status in this setting, likely influences the associations with the genotype with the risk of CVD. Further studies to validate our findings in this population are required.

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81. SARS-CoV-2 RNAemia and Disease Severity in Pediatric Coronavirus Disease 2019 (COVID-19)

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**Session:** O-17. Hot Topics in Pediatric Viral and Fungal Infections

**Background.** Children with COVID-19 may develop severe disease. In hospitalized adults, detection of plasma SARS-CoV-2 RNAemia ranges from 19% to 42% and has been associated with worse clinical outcomes. A similar association in children remains unexplored. We determined the frequency of SARS-CoV-2 RNAemia in children hospitalized with COVID-19 and evaluated its potential association with severe disease.