SARS-CoV-2 triggering severe ARDS and secondary HLH in a 3-year-old child with Down syndrome

Sarah Kim-Hellmuth[1,*], Matthias Hermann[2,*], Julia Eilenberger[1], Julia Ley-Zaporozhan[3], Marcus Fischer[2], Fabian Hauck[1], Christoph Klein[1,4], Nikolaus Haas[2], Matthias Kappler[1], Johannes Huebner[1,4], André Jakob[2], Ulrich von Both[1,4,#]

* These authors contributed equally to this work.

1 Dr von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-University (LMU) Munich, Lindwurmstrasse 4, 80337 Munich, Germany.

2 Department of Paediatric Cardiology and Paediatric Intensive Care, University Hospital, Ludwig-Maximilians-University of Munich, Marchioninistr. 15, 81377 Munich, Germany

3 Department of Radiology, Pediatric Radiology, University Hospital, Ludwig-Maximilians-University (LMU) Munich, Lindwurmstrasse 4, 80337 Munich, Germany.

4 German Centre for Infection Research (DZIF), partner site Munich, Munich, Germany.

[#] Corresponding author:

Ulrich von Both, M.D., FRCPCH

Division of Paediatric Infectious Diseases, Dr von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-University (LMU) Munich, Lindwurmstrasse 4, 80337 Munich, Germany. ulrich.von.both@med.uni-muenchen.de

Abstract

Down syndrome (DS) predisposes to severe immunologic reaction secondary to infectious triggers. Here we report a paediatric DS patient with COVID-19 who developed a hyperinflammatory syndrome, severe ARDS and secondary HLH requiring PICU admission and treatment with steroids, IVIG and Remdesivir. Investigations into genetic susceptibilities for COVID-19 and SARS-CoV-2-associated complications warrants systematic clinical and scientific studies.

Key words: Down syndrome, hyperinflammation, sHLH, Remdesivir, paediatrics

On March 11, 2020, the World Health Organization (WHO) announced Coronavirus disease 2019 (COVID-19) a pandemic. Healthcare professionals have since been caring for increasing numbers of severely sick patients. Children have been reported to be at greatly reduced risk to contract the disease and have usually presented with milder forms of COVID-19 compared to adults. Although children appear to have a low observed case rate of COVID-19, they may still have similar SARS-CoV-2 infection rates compared to adults. So far, no clear predisposing clinical condition for progression of SARS-CoV-2 infection to COVID-19 has been identified in children while severity of disease has been shown to be associated with underlying comorbidities [1]. In addition, reports have highlighted unprecedented clusters of children presenting with Multisystem Inflammatory Syndrome in Children (MIS-C) [2] with some features resembling Kawasaki disease or toxic shock syndrome [3]. In this context, the Royal College of Paediatrics and Child Health (RCPCH) has published a case definition and guidance for clinicians in the UK and worldwide [2]. Patients with Down syndrome (DS) and DS-associated comorbidities are at higher risk for severe clinical manifestations of respiratory infections. While a few recent case reports have detailed COVID-19 in paediatric DS patient [4,5] none have focused on the immunological features associated with COVID-19 in DS patients. Here we present a case of COVID-19-triggered secondary haemophagocytic lymphohistiocytosis (sHLH) in a child with DS.

Case Presentation:

End of March 2020, a 3-year-old boy of central African descent with DS, previously repaired atrioventricular septal defect (AVSD), pulmonary hypertension, and a history of recurrent episodes of bronchitis presented to our paediatric accident & emergency department (A&E). His AVSD had been corrected at 9 months of age and he was subsequently treated for residual pulmonary hypertension for a period of 8 months; following treatment he had no further cardiac issues. Immunisations were all up to date. The child presented with a three-

day history of fever of up to 40 degrees Celsius, increased work of breathing, progressive respiratory distress and cough. On admission he was in distress with persistent cough, moderate tachypnoea (respiratory rate of 45/min), jugular and intercostal recessions, and had an oxygen saturation of 95% in room air, though normal capillary refill. On auscultation he had marked expiratory rhonchi and coarse bilateral crackles. Initial CXR showed extensive bilateral ground-glass opacities in the perihilar and pericardial regions and in the left basal lung obscuring the left hemi diaphragm (Figure 1). Laboratory parameters showed haemoglobin (Hb) 10.1 g/dl, increased neutrophil count of 6.84 Gs/l, C-reactive Protein (CRP) 142 mg/l, procalcitonin (PCT) 22.8 ng/ml and aspartate aminotransferase (AST) 76 U/l. He was started on IV fluids, empiric antibiotic therapy (IV Ampicillin 650 mg q8H, IV Azithromycin 120 mg q24H) and oxygen supply via nasal prongs (1L 100% oxygen). He tested PCR-negative for RSV and influenza A/B and a blood culture taken on admission yielded no bacterial growth. SARS-CoV-2 was detected by PCR from a nasal/throat swab and he was placed in isolation. An illustration of the entire clinical course and a selection of relevant laboratory parameters are shown in Figure 1. On day 4 he suddenly developed markedly increased tachypnea (RR 100/min) and rapidly decreasing oxyhaemoglobin saturations thus requiring oxygen enrichment (6L flow of 100% oxygen). A chest CT scan showed bilateral patchy airspace consolidations with bronchoaerogram and few adjacent ground-glass opacities, relative sparring of the subpleural areas and small pleural effusion (Figure 1). These are atypical features for COVID-19 lung disease but could also be interpreted as severe atypical pneumonia. In comparison with the initial CXR there was marked progression of previous findings and new consolidations in the upper lung regions. Testing for additional bacterial and viral respiratory pathogens, including *Mycoplasma spp.,* by PCR from nasopharyngeal secretions yielded a negative result. In the light of a severe acute respiratory distress syndrome (ARDS) he was transferred to the paediatric intensive care unit (PICU), intubated and put on continuous invasive mechanical ventilation (CMV) for a period of 8 days and he received intermittent prone positioning. On day 5 and 6 the child showed signs of significant inflammation (CRP 136 mg/l, PCT 4.2 ng/ml, IL-6 575 pg/ml), a

sick thyroid syndrome (fT4 0.8ng/dl, fT3 1.3 pg/ml, normal TSH) and signs of sHLH characteristic of a cytokine storm (Hb 7.8 g/dl, platelets 84,000/mm^3, WBC 9,220/mm^3, triglycerides 151 mg/dl, AST 108 U/l, soluble IL-2 receptor 2702 kU/l, fibrinogen 454 mg/dl, ferritin 7499 ng/ml). The latter can be summarised in the HScore, a score for the diagnosis of reactive hemophagocytic syndrome [6] (Table 1). In contrast, patient and clinical features characteristic for MIS-C such as older age, gastrointestinal symptoms, rash or conjunctivitis were missing. There were no signs of cardiac or coronary involvement on repeated echocardiography while the child was treated on PICU; however, a tricuspid regurgitation with a peak pressure of 60-70 mmHg was observed on day 4 of the illness indicating development of a novel moderate pulmonary hypertension during his stay on PICU. Ampicillin was escalated to piperacillin/tazobactam (1.3 g q8H) in view of rapid clinical deterioration and the boy was started on remdesivir (5 mg/kg loading dose, followed by 2.5 mg/kg OD) via a compassionate use program. Upon diagnosis of sHLH according to HScore, immunosuppressive / immunomodulatory therapy was initiated with prednisolone (2mg/kg OD) and the boy received a single dose of intravenous immunoglobulin (IVIG) (1g/kg). Evaluation of the gene expression pattern of interferon-stimulated genes on day 8 demonstrated a profound activation of the type-I-IFN response. Over the next few days, the clinical condition gradually improved allowing weaning from invasive CMV on day 12. Remdesivir was continued for a total of 9 days; steroids were also weaned and eventually discontinued on day 17. He had normal oxygen saturation on room air on day 16 and displayed gradual normalisation of pulmonary arterial pressure from day 9 onwards. While slowly re-establishing oral feeds and with continuous physiotherapeutic support, the child was discharged home 22 days after admission. A CXR at discharge demonstrated only very mild residual peribronchial opacities in pericardial regions, correlating well with the clinical recovery. Six weeks after discharge he continued to be well and his laboratory parameters had normalised.

Discussion:

Our patient illustrates a case of severe pulmonary COVID-19 triggering sHLH. Patients with Down syndrome show a consistently activated signalling cascade in the IFN pathway [7], which may have predisposed our patient to progress to sHLH. Trisomy 21 has been demonstrated to activate the IFN transcriptional response in a number of human cell lines, including monocytes and T cells [7]. Hence, children with Down syndrome might be at increased risk for developing sHLH in the context of various infectious triggers as documented in a few case reports [8,9], including viruses such as SARS-CoV-2. Secondary HLH is a life-threatening condition that has some features in common with MIS-C such as persistent fevers, abnormal blood cell counts and inflammatory markers. However, it is important to note that inflammatory markers such as ferritin, fibrinogen, and AST do not reach the levels of sHLH patients [10]. In addition, MIS-C commonly affects older children and gastrointestinal symptoms such as abdominal pain, vomiting and diarrhoea as well as myocardial dysfunction are very common. These characteristics were all missing in our patient. While MIS-C patients frequently present with symptoms of shock and multi-organ failure, our patient first presented with symptoms consistent with COVID-19, cough and respiratory distress. He subsequently deteriorated – similar to adult-type COVID-19 - and developed severe ARDS and a type-I-IFN-driven hyperinflammatory condition with sHLH. Treatment regimens for hyperinflammatory states and sHLH may include IVIG and corticosteroids as well as monoclonal antibodies such as tocilizumab. We chose administering steroids instead of tocilizumab because of their broader pharmacodynamic capacity. Of note, a recent meta-analysis highlighted that the administration of systemic corticosteroids in critically ill COVID-19 patients was associated with lower all-cause mortality [11], while tocilizimab was not effective for preventing death in moderately ill COVID-19 patients [12]. In general, it is critically important that in cases of suspected sHLH immediate analysis of key laboratory parameters is initiated, such as haemoglobin, white

blood cell and platelet counts, triglycerides, AST, ferritin, fibrinogen as well as soluble IL-2 receptor.

This case illustrates that further clinical and scientific investigations into genetic susceptibilities impacting severity of COVID-19 and SARS-CoV-2-associated complications are needed. While systematic epidemiological data on COVID-19 in paediatric DS patients is clearly lacking, we intend to highlight this particular hyperinflammatory and life-threatening presentation of a child with DS to the wider paediatric community to ensure early clinical recognition of similar cases in the ongoing SARS-CoV-2 pandemic.

Acknowledgements:

We thank clinical and nursing staff for excellent care and colleagues at the university hospital Dresden for performing RNA profiling of IFN-stimulated genes.

References:

1 Bellino S, Punzo O, Rota MC, *et al.* COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. *Pediatrics* 2020;**146**:e2020009399. doi:10.1542/peds.2020-009399

2 Royal College of Paediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: *https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf.* Accessed Sept 10, 2020.

3 Riphagen S, Gomez X, Gonzalez-Martinez C, *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;**395**:1607–8. doi:10.1016/S0140-6736(20)31094-1

4 Newman AM, Jhaveri R, Patel AB, *et al.* Trisomy 21 and Coronavirus Disease 2019 in Pediatric Patients. *The Journal of Pediatrics* 2020;:1–4. doi:10.1016/j.jpeds.2020.08.067

5 Krishnan US, Krishnan SS, Jain S, *et al.* SARS-CoV-2 Infection in Patients with Down Syndrome, Congenital Heart Disease, and Pulmonary Hypertension: Is Down Syndrome a Risk Factor? *The Journal of Pediatrics* 2020;**225**:246–8. doi:10.1016/j.jpeds.2020.06.076

6 Fardet L, Galicier L, Lambotte O, *et al.* Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;**66**:2613–20. doi:10.1002/art.38690

7 Sullivan KD, Lewis HC, Hill AA, *et al.* Trisomy 21 consistently activates the interferon response. *eLife* 2016;**5**:1709. doi:10.7554/eLife.16220

8 Lazea C, Blag C. Hemophagocytic Lymphohistiocytosis Secondary to Mycoplasma Pneumoniae Infection in a Trisomy 21 girl. *Revista Romana de Medicina de Laborator* 2018;**26**:113–7. doi:10.1515/rrlm-2017-0039

9 Lee HJ, Lee MJ, Kim S-J, *et al.* Hemophagocytic lymphohistiocytosis in adults. *Korean J Anesthesiol* 2014;**67**:S115–7. doi:10.4097/kjae.2014.67.S.S115

10 Whittaker E, Bamford A, Kenny J, *et al.* Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA* 2020;**324**:259–11. doi:10.1001/jama.2020.10369

11 WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, *et al.* Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020;**324**:1330–41. doi:10.1001/jama.2020.17023

12 Stone JH, Frigault MJ, Serling-Boyd NJ, *et al.* Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med* Published Online First: 21 October 2020. doi:10.1056/NEJMoa2028836

Figure legend:

A. Timeline of the clinical course including diagnostic procedures and treatment regimens. Abbreviations: +, positive; –, negative; CXR, chest X-ray; CT, Computed Tomography; PICU, paediatric intensive care unit; CMV, continuous mechanical ventilation; IVIG, intravenous immunoglobulin. Of note, on day 8 both the SARS-CoV-2 PCR as well as the anti-SARS-CoV-2 IgA/IgG Elisa were performed.

B. Time course of a selection of clinical parameters. Dashed lines indicate either the upper and lower normal range when two lines are shown (WBC, Lymphocyte count, Ferritin, LDH) or the normal threshold when one line is shown (CRP, IL-6, PCT, AST).

C. Left image: Initial (day 1) chest X-ray (erect posterior-anterior view) shows central bronchial wall thickening, bilateral ground-glass opacities in perihilar and pericardial lung regions and basal consolidations on the left. Left diaphragm and left lower margin of the heart are obscured. Cardiac right margin cannot be clearly delineated. Mild blunting of the right costo-phrenic angle. Two metal clips in the left mediastinum after surgical closure of patent ductus arteriosus. These findings are suggestive for severe bronchopneumonia.

Right image: Coronal reformatted CT image on day 4 showing marked disease progression. Extensive patchy and confluent consolidations with bronchoaerogram in lower lung and new involvement in upper lung regions. Relative sparing of the subpleural regions except for the left lower lobe.

Table 1 legend:

Table 1. HScore for secondary HLH by clinical parameters. Patient's parameters and corresponding point are highlighted in red.

	Number of points
Temperature (˚C)	
<38.4	0
38.4 – 39.4	33
>39.4	49
Organomegaly	
None	0
Hepato- or splenomegaly	23
Hepato- and splenomegaly	38
Number of cytopenias	
One lineage	0
Two lineages	24
Three lineages	34
Ferritin (ng/ml)	
<2000	0
2000 – 6000	35
>6000	50
Triglycerides (mg/dL)	
<132.7	0
132.7 – 354	44
>354	64
Fibrinogen (mg/dL)	
>250	0
≤250	30
Serum aspartate aminotransferase (IU/L)	
<30	0
≥30	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression	
No	0
Yes	18
Total Hscore	**216**
>169 accurately classifies 90% of patients with HLH	

Table 1. HScore for secondary HLH by clinical parameters. Patient's parameters and corresponding point are highlighted in red.

Figure 1