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LETTER TO THE EDITOR

Reduced incidence of hemophagocytic lymphohistiocytosis in Japan during the COVID-19 pandemic

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Hemophagocytic lymphohistiocytosis (HLH) has two distinct forms: primary HLH, which is a genetic disorder, and secondary HLH, which is due to infection, malignancy, autoimmune disorder, or stem cell transplantation. Ishii et al. [1] reported that 68.8% of patients diagnosed with HLH in Japan were under 30 years of age. The most frequent cause of HLH was Epstein–Barr virus (EBV). The sum of EBV-associated HLH (EBV-HLH) and other infection-associated HLH accounts for 53.1% of the total incidence of HLH in Japan. Development of primary HLH may also be triggered by infection. Thus, infectious etiologies are the main cause or trigger of HLH, especially in young children and adolescents.

In December 2019, the coronavirus disease 2019 (COVID-19) pandemic hit Japan [2]. Precautionary measures including proper handwashing, wearing of facemasks, and closure of schools were implemented to control the spread. The National Institute of Infectious Disease of Japan revealed that a majority of common infectious diseases (influenza, hand–foot and mouth disease, herpangina, infectious gastroenteritis, and respiratory syncytial virus infection) also markedly decreased in 2020 (during the COVID-19 pandemic).

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We hypothesized that these changes in lifestyle and infectious disease incidence during the COVID-19 pandemic may have affected the incidence of HLH. Therefore, we assessed the incidence of six hematological diseases, namely HLH, infectious mononucleosis (IM), acute immune thrombocytopenia (aITP), Langerhans cell histiocytosis (LCH), acute lymphoblastic leukemia (ALL), and mature B cell lymphoma (B-NHL), before and during the COVID-19 pandemic (2018 to 2020). We analyzed the public dataset from the Blood Disease Registration maintained by the Japanese Society of Hematology (JSH). This dataset aggregates data from the JSH, Japanese Society of Pediatric Hematology and Oncology (JSPHO), and National Hospital Organization. From 2016 to 2019, the mean number of patients registered was $42{,}406 \pm 5{,}046$. In 2020, this figure was 46,471. To analyze changes in annual incidence, we calculated the mean and standard deviation for the 2016–2019 data, and compared this to the annual incidence of each disease in 2020.

The analyzed data are summarized in Table 1. The total incidence of HLH decreased to 73.7%, compared with the 2016–2019 mean incidence of HLH (152 vs. 206.3 ± 10.2). Furthermore, HLH incidence in 2020 decreased by 77.5% in those less than 20 years old, and 77.9% in those over 20 years old. Similarly, the incidence of IM and aITP decreased by 91.5% and 78.4% in 2020, compared to the respective mean incidences of IM and aITP from 2016 to 2019. The decrease in the number of IM and aITP patients was larger among those less than 20 years of age, compared to those 20 years of age or older (IM: 84.8% vs. 96.6%, and aITP: 52.6% vs. 106.5%). On the other hand, the incidences of LCH, ALL, and B-NHL did not decrease in 2020 (LCH, 109.9%; ALL, 102.9%; and B-NHL, 111.9%).

Our data revealed that the incidence of HLH decreased during the COVID-19 pandemic. We observed a similar trend in patients with IM and aITP. Various infectious diseases have dramatically decreased during the COVID-19 pandemic. In Japan, the most frequent cause of HLH in

Table1 The incidence of hematological disease before and during COVID-19 pandemic

Disease	2016 (*N*)	2017 (*N*)	2018 (*N*)	2019 (N)	2016–2019 (*N*, Mean ± SD)	2020 (*N*)	Rate of change (%)
Total							
HLH	219	209	195	202	206.3 ± 10.2	152	−26.3
IM	289	248	324	415	319.0 ± 71.1	292	−8.5
aITP	647	520	448	497	528.0 ± 84.8	414	−21.6
LCH	94	89	102	90	93.8 ± 5.9	103	+9.9
ALL	865	1152	1056	1083	1039 ± 123	1069	+2.9
B-NHL	15,472	17,005	19,239	20,474	18,047 ± 2238	20,198	+11.9
Under 20 years							
HLH	97	79	65	75	74.8 ± 13.3	58	−22.5
IM	68	83	109	122	92.0 ± 20.2	78	−15.2
aITP	364	311	174	181	230.2 ± 91.6	121	−47.4
LCH	82	78	88	77	79.8 ± 4.8	74	−7.3
ALL	473	512	445	446	459.2 ± 31.3	420	−8.5
B-NHL	125	105	96	88	101.2 ± 13.2	92	−9.1
Over 20 years							
HLH	122	130	130	127	120.6 ± 13.6	94	−22.1
IM	221	165	215	293	221.6 ± 41.0	214	−3.4
aITP	283	209	274	316	275.0 ± 35.8	293	+6.5
LCH	12	11	14	13	15.8 ± 6.7	29	+83.5
ALL	392	640	611	637	585.5 ± 97.7	649	+10.8
B-NHL	15,347	16,900	19,143	20,386	18,376 ± 1948	20,106	+9.4

HLH hemophagocytic lymphohistiocytosis, *IM* infectious mononucleosis, *aITP* acute immune thrombocytopenia, *LCH* Langerhans cell histiocytosis, *ALL* acute lymphoblastic leukemia, *B-NHL* mature B cell lymphoma

children and adolescents and young adults was infection, while malignancy (lymphoma)-associated HLH was the main cause of HLH in adults [1]. Thus, the annual incidence of HLH during the COVID-19 pandemic decreased due to a decrease in infectious triggers. EBV, which is the most frequent cause of HLH in Japan, is transmitted through saliva. Similar to EBV infection, the majority of these infections spread through contact and respiratory aerosol transmission. Lifestyle changes implemented during the COVID-19 pandemic, specifically social distancing, wearing of facemasks, alcohol disinfection, and school closure, effectively reduced contact and droplet transmission. The fact that incidence of IM and aITP also decreased during the COVID-19 pandemic decreased, especially in those younger than 20 years old, supports this hypothesis. Both IM and aITP are triggered by infection, and the majority of the cases occur in those less than 20 years old. In contrast, the incidence of LCH, ALL, and B-NHL, which are not triggered by infection, did not change during the COVID-19 pandemic.

This limitation of this report is as follows. First, the analyzed data from the Blood Disease Registration maintained by JSH were total numbers of HLH (both primary and secondary). Additionally, severe COVID-19 patients present with persistent fever, pancytopenia and multiorgan dysfunction, known as multisystem inflammatory syndrome (MIS) [3]. Several reports have indicated a close relationship between MIS and HLH [4, 5]. Unfortunately, we could not obtain detailed information of causes of HLH before and during the COVID-19 pandemic, such as infection (including COVID-19), malignancy, or autoimmune disease. Second, we could not perform sufficient statistical analysis because we only analyzed annual numbers of patients with each disease over a five-year period (2016–2020). Finally, the observation period was too short. Since vaccination against COVID-19 for those over 12 years of age began in February 2021 in Japan, we could not analyze the effect of vaccination on the incidence of HLH, IM, and aITP. Further studies are required to clarify the association between the incidence of HLH and the COVID-19 pandemic.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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