

## LETTER

## Acute Leukemia in children after recent COVID-19 infection. Possible association?

Dear Editor,

Children with Covid-19 infection have been reported as asymptomatic or mildly infected compared to adults<sup>1</sup>, but late consequences or complications have not been clearly recognized yet.

In the pediatric population, hematologic malignancies constitute the most common neoplastic diseases, with acute leukemia (AL) occupying first place with a rate of 32.8 %<sup>2</sup>. Several etiologic factors have been suggested to cause AL. Such a hypothesis by Greaves<sup>3</sup>, suggests that acute lymphoblastic leukemia (ALL) develops in two distinct steps. The first step occurs in utero with a generation of a pre-leukemic clone that may contain genetic mutations associated with leukemia. The second one occurs postnatally by exposing a susceptible child to a common infectious agent (a virus). According to this hypothesis, the infectious agent triggers an overstimulated immune response in the preleukemic clone population leading to leukemia cells' proliferation. Another analysis by Bartenhagen et al<sup>4</sup> detected viruses in sporadic cases of acute childhood B-precursor ALL using whole-genome sequencing, and analyses suggest that the requested factor could be a common virus or another infectious agent.

Measures implemented to control the spread of Covid-19 (social distancing, self-isolation, etc.) may, therefore, lead to a reduced number of ALL cases in the near future<sup>5</sup>. However, infection of predisposed children to Covid-19 may serve as a second trigger step in the Greaves hypothesis.

We report three children with AL who were admitted to our Unit a few weeks after Covid-19 infection. The first patient, a 10-year-old girl, presented with fever, weakness, anemia, and thrombocytopenia. Bone marrow (BM) aspiration confirmed the diagnosis of B-ALL with normal karyotype. One month before admission, she got sick from Covid-19, with positive serology. Secondly, a 3.5-year-old girl was admitted with fever and splenomegaly. Blood tests revealed anemia, neutropenia, and thrombocytopenia, and she was diagnosed with B-common ALL. *RUNX1* expression was detected in the karyotype and was confirmed by fluorescence in situ hybridization (FISH). Positive serum antibodies for Covid-19 were found. Finally, a 6-month-old baby girl was hospitalized due to extreme leukocytosis, anemia, and thrombocytopenia. There was no history of hematologic disorder or infection. BM immunophenotype set the diagnosis of AML-M7, and chromosomal analysis showed monosomy 7 and trisomy 19. Serology was positive for previous Covid-19 infection.

We cannot lead to a causal link between the Covid-19 infection and the subsequent AL diagnoses. However, our observations are consistent with the Greaves hypothesis as described above. Publication of these cases may help to elucidate a possible link between Covid-19 infection and acute leukemia in children, and ongoing epidemiological surveillance should examine this relationship.

**Keywords:** Acute leukemia, acute lymphoblastic leukemia, children, Covid-19 infection, immune response

**Conflict of interest**

There are no conflicts of interest to report.

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