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EDITORIAL

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Have COVID-19 affected ALL epidemiology?

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer in the Nordic countries with an incidence of approximately 4.0 per 100.000 children per year.[1] An incidence peak is found in the two to seven years age group with a peak at three years of age, where the incidence is up to 10 times higher than in infancy or among adolescent. Almost eighty per cent of the B-cell precursor (BCP) ALL cases, which constitutes the age-related incidence peak, harbour either an *ETV6/RUNX1*-translocation or a high-hyperdiploid leukaemic clone.[2] Both these subsets are frequently initiated prenatally and 5% of newborns may harbour preleukaemic cells in their cord blood,[3,4] which emphasises their long subclinical phase.

A small proportion of ALL cases can be attributed to a strong genetic predisposition,[5] while the vast majority are caused by a complex interaction between common germline variants,[6,7] environmental factors such as infections and random events due to the massive expansion of our immune system in early life. Infectious exposures in early life and the associated modulation of our microbiome structure promote normal immune system maturation[8] and may accelerate the disappearance of preleukaemic cells and thus influence the subsequent risk of ALL,[9,10] while infections that induce a strong proliferative immune response on the other hand could lead to overt leukaemia.[3]

An increased incidence of childhood infections in general has been observed during the months prior to the diagnosis of ALL,[11] but whether this reflects infection-induced proliferation of a dormant preleukaemic cell population or a leukaemia-induced immune deficiency (reverse causality) is unknown. In industrialised countries, febrile infections in children frequently lead to prescription of antibiotics and the associated disturbance of the gut microbiome could also promote leukaemia development as recently supported by leukaemia-prone murine models.[12]

In this issue of Acta Pædiatrica, Jarvis and co-workers present observational data indicating a significant reduction in the incidence of childhood ALL in the Oslo region (South-Eastern Norway; ~2.6 million inhabitants) during the Norwegian lockdown response to the COVID-19 pandemic.[13] Thus, during the first six months of 2020 only three cases (including two in early March) were diagnosed, with no cases during the four months from March 13th to July 12th, which is significantly below the expected ALL incidence based on historical data ($P < .001$). During the same time period, the authors also observed a drop in airway pathogens found by PCR, although the number of performed tests did not change markedly compared to historical data.

As the COVID-19 challenge to health care systems worldwide is influenced by the magnitude of the spread and the local healthcare resources, referral of childhood cancer patients has been reported being stalled in very challenged regions with more advanced disease being diagnosed later by some.

In this context, the paper by Jarvis et al is of interest, as the health care system in Norway, was never seriously burdened by COVID-19 to the same extent as many other healthcare regions in Europe and the US and also due to the free access to health care in Norway. Thus, a reduced number of diagnosed ALL cases in Oslo could potentially reflect a real change in incidence. Such a reduction in ALL incidence has similarly been reported in Hongkong during the SARS epidemic in 2003, while flu epidemics have been associated with sharp peaks in cases of ALL in the United Kingdom.[14] Still, the data reported by Jarvis et al need to be interpreted very cautiously:

1. Although no new ALL cases in a four-month period may seem convincing and an overall reduced burden of infections could potentially affect the incidence of ALL, this would never drop to zero overnight and similarly normalise abruptly.
2. As the clonal expansion of ALL and the associated exhaustion of the normal bone marrow function leading to pancytopenia are relatively slow (weeks to months), a much longer observation period would be needed, as well as an comparison of ALL demographics across the Nordic countries, since Sweden (twice the population of Norway) has differed from most of the rest of the world by not implementing a nation-wide COVID-19 lockdown.
3. The pathogenesis of childhood ALL subtypes is not uniform, and host DNA variants have been associated with one subtype rather that another. Thus, it would be of interest in a larger (international) data sets to explore, which lineage (BCP- vs T-ALL) and cytogenetic subtypes were most affected by the lockdown, and if simple clinical characteristics such as age, haemoglobin and white blood cell count at diagnosis differed from the usual pattern.
4. If infections during the months preceding the diagnosis of ALL are causative rather than a consequence of the haematological malignancy, a more detailed analysis of degree of lockdown, the overall pattern of childhood infections, hospital admission and use of antibiotics during the months preceding ALL would be of interest.[11,12]
5. The risks of type 1 error and publication bias are emphasised by the initial reporting of another unexpected beneficial health

consequence of COVID-19, *that is*, the drop in extremely premature births that was later refuted by a much larger data set.[15] Until similar expanded larger data sets are available for childhood ALL, the potential impact on childhood ALL incidence by massive reduction in the infectious burden remains uncertain.

CONFLICT OF INTERESTS

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