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SPECIAL REPORT

Leukaemia and lockdown: The delayed infection model of childhood acute lymphoblastic leukaemia and the COVID-19 pandemic

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Abstract

Acute lymphoblastic leukaemia (ALL) is the most common type of leukaemia diagnosed in children. The prevailing hypothesis regarding pathogenesis of childhood ALL was developed by Greaves, and states that ALL is caused by an abnormal immune response to a common infection. The response arises either due to naivety of the immune system caused by a lack of common childhood infections, or genetic susceptibility due to specific alleles. The former explanation is known as the delayed infection hypothesis. COVID-19 is a new infection that no children in the UK were exposed to prior to 2020. Furthermore, the lockdown measures designed to prevent spread of this virus have also greatly reduced spread of other common infections. It is therefore important to examine the evidence for this hypothesis, and to consider it in the context of the pandemic to determine what effect lockdown measures may have on incidence of ALL in children.

KEYWORDS
ALL, COVID-19, delayed infection hypothesis

1 | INTRODUCTION

The most prominent theory of how childhood B-cell precursor acute lymphoblastic leukaemia (ALL) arises was first proposed by Greaves in 1988.[1] The 'two hit' hypothesis suggests that ALL arises after two separate events have occurred. The first is a mutation in utero leading to fusion gene formation or hyperdiploidy. This generates a preleukaemic clone, which becomes overt ALL when an environmental factor in childhood triggers secondary genetic changes. In the case of ETS translocation variant 6 (ETV6)–runt-related transcription factor 1 (RUNX1) + ALL, these secondary mutations are primarily V(D)J recombination-activating protein and activation-induced cytidine deaminase-driven copy number alterations. This delayed infection model is based on the evolutionary argument that immune cells were programmed by events from all previous generations to pre-empt infections in infancy and that exposure to these infections is essential for development of a functional adaptive immune system in adulthood.

The exact genetic mechanisms that lead to disease are poorly understood. The in utero events are clearly necessary, but insufficient to cause ALL alone. Gestational and genetic factors are thought to influence development of a 'first hit', whereas exposures after birth are thought to supply the 'second hit'. The vast majority of childhood ALL cases are not explained by known predisposing genetic abnormalities such as Bloom's syndrome or Li-Fraumeni; rather, susceptibility is likely influenced by the co-inheritance of multiple low-penetrant variants, each associated with modestly increased risk. These are likely to have varying effects on ALL risk depending on cellular phenotype. This is the case with ARID5B and PIP4K2A variants, which are linked with the risk of developing hyperdiploid ALL.[2] The single-nucleotide polymorphisms in these genes are so far lacking a clear function, therefore the molecular mechanisms by which these variants are linked to ALL risk are unknown.

Abbreviations: ALL, acute lymphoblastic leukaemia; BCP-ALL, B-cell precursor acute lymphoblastic leukaemia; COVID-19, coronavirus disease 2019; ETV6, ETS translocation variant 6; RUNX1, runt-related transcription factor 1.

2 | EVIDENCE FOR THE DELAYED INFECTION MODEL

The first suggestion that infections could play a role in the pathogenesis of childhood leukaemia came in the early 20th century because the age distribution of leukaemia and common infections was similar, and many children had infections immediately preceding their diagnosis of leukaemia.[3] Although suggestions made at that time that specific infections were the trigger for leukaemia have now been disproven,[4] there is a substantial body of evidence supporting Greaves' hypothesis. The UK Children's Cancer Study Group (UKCCS) was founded in the 1990s and it investigated potential causes of childhood ALL including ionising and non-ionising radiation, chemical exposure and infection. Nursery attendance was used as one surrogate measure for infection, as the increased number of infections in children attending nursery was well known.[5] A significant protective impact of nursery attendance before 1 year of age, and therefore catching common infections during that time, was found against ALL overall and B-cell precursor acute lymphoblastic leukaemia (BCP-ALL).[6] The same protection was not seen for AML or any other paediatric cancer, which makes it highly unlikely that the results seen for ALL were confounded by social factors or other variables.

Evidence from monochorionic twins has shed significant light on factors that determine the progression of a preleukaemic clone to overt ALL. When twins are monochorionic, vascular anastomoses allow blood cell chimerism to arise between the twins. The suggestion that leukaemia in identical twins could be due to an in utero mutation in one twin that then spreads to the other, rather than shared genetic susceptibility, was first made in 1962 and then investigated fully in 1971.[7] Since then, several studies have shown that in monochorionic twins where only one develops BCP-ALL, the healthy twin has a population of covert preleukaemic cells with the same mutation. Hong et al. investigated a pair of female monochorionic twins where one was diagnosed with TEL-AML1-positive pre-B-cell ALL at age 2, and the other remained clinically normal. The healthy twin also had small numbers of TEL-AML1-positive B lineage-affiliated CD19+ cells in peripheral blood, but these cells all contained a normal TEL allele, consistent with preleukaemic status.[8]

Situations in which large-scale societal changes happen rapidly often provide very interesting data. An example of such a time is the reunification of Germany in 1989, when many aspects of life in the former East Germany were transformed almost overnight. After the reunification, incidence of childhood ALL in the old East Germany increased by 25% in only 6 years, compared to a 1% increase per year in former West Germany and the rest of Europe over the same period.[9] This level of change was not seen for AML or childhood solid cancers, and as East Germany already had a robust reporting system, the change is unlikely to be due to an improvement in reporting. Spix et al. ascribed this enormous rise to the abrupt change in nursery attendance after 1989. In East Germany, almost all babies attended state day care centres from 3 months old so that their mothers could work. This immediately ceased upon reunification, and the prediction that these children who did not attend day care in their first year of life would be at higher risk of ALL was proved right when they reached 3–5 years of age. The higher incidence of ALL in former East Germany after the reunification is almost certainly due to the discontinuation of universal nursery attendance, demonstrating that a naive immune system increases the likelihood of overt ALL developing from the preleukaemic clone.

In addition to these large-scale epidemiological studies, in-depth analysis of small clusters of ALL can also provide evidence for the delayed infection hypothesis. A significant cluster of BCP-ALL was recognised in Milan in 2017.[10] Seven children were diagnosed across a 4-week period, four of whom lived in the same area, and three of those four attended school together. No association with ionising or non-ionising radiation or chemical exposure was found, however all seven patients had contracted the AH1N1 swine flu virus 3–6 months previously. Six of the seven were also firstborn children, and none attended nursery in the first year of life. This was the first report linking such a cluster to a specific viral infection; peaks in the incidence of childhood ALL have been observed in the UK around 6 months after seasonal influenza epidemics in 1976 and 1990.[11] Of course, this is just a small study, but the features of this cluster serve to corroborate the protective effect of infections early in life, and the effect of exposure to these infections for the first time during the peak age for ALL.

3 | COVID-19 AS THE SECOND HIT

In the context of the delayed infection hypothesis, it is only logical to wonder whether coronavirus disease 2019 (COVID-19) infection can act as the second hit. It has been well documented that children are not usually badly affected by the infection itself[12]; however, the consequences of infection for the small percentage of children with a preleukaemic clone could be catastrophic. The first indication that COVID-19 could interact with lymphocytes in such a way as to give rise to leukaemia came late in 2020 when Largeaud et al. reported a massive expansion of a chronic lymphoid leukaemia clone in a patient with COVID-19.[13] On day 11 of the patient's treatment for COVID-19, a blood count showed an increased number of lymphocytes, which triggered a full immunophenotype investigation to be carried out. A small CD5+ CLL-type clone was identified, which expanded significantly during the patient's treatment in ICU. Five months later, the full blood count was normal with no lymphocytosis, although the CLL-type clone was still detectable in small numbers. This case suggested that SARS-CoV-2 may have a previously unrecognised indirect effect on lymphocytes. The authors suggested that this may be due to cytokine stimulation, as it resolved rapidly after the infection was cleared. Although this is just one case, and CLL is clearly a different disease to childhood ALL, this report is nonetheless important in demonstrating that COVID-19 has been observed to interact with lymphocytes to cause rapid clonal proliferation.

Following the publication of this case, a case of ALL was reported in a 9-year-old boy who had been exposed to COVID-19 less than 4 weeks previously.[14] There was no clinical evidence of leukaemia in the patient when he was initially hospitalised with COVID-19, and the full blood count was normal. However, 7 days after discharge he was reassessed

for bone pain and anorexia, and near-complete replacement of the bone marrow with lymphoblasts was discovered. Immunophenotyping was consistent with BCP-ALL. As the second hit in the delayed infection hypothesis is thought to be a pathogen to which the child has not previously been exposed, it makes sense that a novel virus such as SARS-CoV-2 would be able to fulfil this role.

Taub and colleagues note that the ETV6–RUNX1 fusion gene has been identified in up to 5% of blood samples from healthy neonates,[15] meaning that there is potential for an enormous rise in childhood ALL during the pandemic, as no children have previously been exposed to this virus. Those who may have previously been low risk for transformation to overt leukaemia due to having several older siblings, or attending nursery in the first year of life will not be afforded protection by those factors against a second hit due to COVID-19, as it is guaranteed that they were not exposed to it as newborns. However, as there are a multitude of pathogens potentially capable of providing the second hit, there are other factors that must be taken into account in order to determine the effect of the pandemic on childhood ALL.

4 | PREVENTION OF A SECOND HIT BY LOCKDOWN MEASURES

It is also possible that the measures taken to prevent the spread of the virus may in fact reduce cases of ALL. This was seen in Hong Kong following the SARS outbreak of 2003. Hong Kong was severely affected by the outbreak, therefore the government took extreme measures to prevent transmission of the virus, very similar to those taken in the UK during the recent periods of lockdown. This included school closures for 2 months, then stringent cleaning regimes, hand-washing campaigns, increased ventilation, and mandatory mask wearing in schools when they reopened. Children therefore caught far fewer seasonal viral infections at school than they normally would, meaning that those who did have a covert preleukaemic clone may have avoided the second hit of infection. This was reflected in the decrease in childhood BCP-ALL cases during the SARS outbreak. Li et al. studied trends in ALL before, during and after the outbreak and found that 2003 had a lower number of ALL cases, which correlated with fewer cases of common infectious diseases such as chickenpox.[16]

It is possible that a similar pattern may be observed following the strict lockdown implemented in the UK, perhaps even to a greater extent than during the Hong Kong SARS outbreak, as the COVID-19 pandemic has lasted much longer. This could result in a significant decrease in children with ALL in the coming year. If so, this raises many important questions about infection prevention steps that are normally taken in schools, and whether there is any benefit to keeping some of the new measures in place, for example more frequent hand washing. One of the limitations of the study that the authors raise is that the population of children in Hong Kong is relatively small, with 1.1 million children younger than 15. Therefore, the usual annual number of new ALL diagnoses in children is only 30–40. By comparison, in the UK there were over 12.5 million children under 16 in 2019.[17] Consequently, any effect caused by the pandemic may be even more obvious in the UK. It will be very interesting to see data about childhood ALL diagnoses during this time as it is published over the next few months and years.

In order to assess the potential impact of the pandemic on childhood ALL, it is not only events occurring during the peak age of ALL incidence that must be considered, but also those in the first year of life. Babies born during the SARS outbreak had far fewer social contacts than those born before or after. In the light of the delayed infection hypothesis, this would put them at greater risk of developing ALL when they are children, as their immune system did not encounter many common infections early in life. The same is true to an even greater degree, for babies born in 2020. Therefore the reduction seen during and immediately after the outbreak may be negated by the later increase once the babies born during that time reach childhood. Li et al reported a notable decrease in the incidence of ALL in Hong Kong 2003, and the authors concluded that this was likely to be as a result of the reduction in childhood infections during the SARS outbreak.[16] In the 2-year period post-outbreak, no increase was seen, however this is to be expected if incidence of ALL is highest in ages 2–6.

A recent paper has reported a reduction in the number of childhood ALL cases in Oslo University Hospital during the COVID-19 pandemic. During the first four months of the lockdown, no new ALL patients were diagnosed. Based on the observed rate in 2017-2019, the probability of this event is <0.001. A decrease of 82% and 76% in PCR-identified airway pathogens in children in April and May 2020 was found, compared to the average for these months in 2017-2019, while the total number of tests carried out remained similar.[18] The authors similarly concluded that, although the absolute numbers were small, the large drop in common infections was likely to play a role in the subsequent drop in ALL cases. Although this is only a small study from one hospital, it is exciting that we are already able to gather evidence to begin to answer these important questions. This provides an interesting starting point for studies carried out following the COVID-19 pandemic to build on when investigating the prevalence of ALL in babies born during the lockdown. This will become all the more relevant when data is available on the rates of ALL in these children once they are older. Data produced in the coming years will be absolutely essential to furthering our understanding of the pathogenesis of this cancer. Many newborns did not encounter anybody from outside of their household for several months, let alone mix with many other children at nursery. It is therefore expected that the majority of babies born in 2020–2021 will have very naive immune systems compared to previous years, which is highly likely to affect how many of these children go on to develop ALL.

5 | CONCLUSION

ALL is the most common childhood cancer, and although there are effective treatments for it, it is not currently preventable. As discussed, there are many factors at play that may lead to an increase or decrease in ALL incidence postpandemic. With these two opposing possibilities in the balance, a rare opportunity to study this disease is presented.

One way to do this would be a prospective cohort study of children known to have been infected with COVID-19, comparing rates of ALL versus an uninfected control group. Once the babies born during the pandemic are school age, there will be much interest in whether the naivety of their immune system as a result of significantly fewer social contacts in infancy will lead to a greater risk of ALL in their childhood. A cohort of babies born in lockdown could also be started and compared against babies born after the lockdown to look for any effect of the expected immune system naivety on ALL incidence. Alternatively, in a similar way to the recent report by Jarvis et al,[18] registry data could be used to study overall ALL rates before, during and after the pandemic to detect larger scale fluctuations.

Our understanding of the pathogenesis of this disease is supported by many epidemiological and genetic studies, all of which have contributed to our ability to treat it. There may not be another chance in our lifetime to study the delayed infection hypothesis in such an enormous cohort as that of the children who experienced lockdown. Therefore, if our aim is to one day prevent childhood ALL, it is essential not to miss this opportunity to further deepen our knowledge of its pathogenesis.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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