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COMMENT

Epigenetic insights into the pathogenesis of Kawasaki disease

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It has been suggested that the prenatal and perinatal environments influence the development of diseases in adulthood. During the Dutch famine of World War II, children exposed to low nutrition in utero during pregnancy showed a high incidence of obesity in adulthood.[1] Various stresses during the fetal period, including preterm birth and low birth weight, increase the future risks of coronary artery disease, stroke, liver disease, hypertension, diabetes, cancer, and chronic kidney disease.[1–3] In addition, it is becoming clear that stresses during the early postnatal period can affect health in later life. This hypothesis, previously known as the Barker hypothesis, has now evolved into the DOHAD (Developmental Origins of Health and Disease) hypothesis. Prenatal and perinatal fetal exposures can induce epigenetic modifications that persist into adulthood and contribute to disease development later in life. Such epigenetic modifications include DNA methylations, histone modifications, and microRNAs that modify gene transcription and expression. Thus, the fetal period and infancy hold the keys to lifelong health. Determination of the relationships between diseases after birth and stresses during the fetal period and infancy is an important field in health-related research. In recent years, epigenetic therapies have been attracting attention as novel treatments for cancer, and in the future, these therapies are expected to prevent and treat various diseases.

Kawasaki disease (KD), a systemic medium-sized vasculitis, is the most frequently acquired heart disease in developed countries. KD is most common in East Asian people, especially Japanese people, because of genetic racial differences. Takeuchi et al.[4] analyzed prenatal and perinatal exposures as risk factors for KD development at 7 to 66 months of age using a Japanese birth cohort, the Longitudinal Survey of Babies in the 21st Century. Because Japan has the highest incidence of KD in the world, at >16,000 cases per year, their study is valuable and unique. Although the study had a limitation of racial genetics, it would be difficult to conduct this kind of epidemiological research outside of Japan. They found for the first time that preterm birth is a significant risk factor for KD. Furthermore, based on the results of their previous study, they revealed that non-exclusionary breastfeeding is a significant risk factor that further increases the risk of KD.[5]

However, when we examine their research design and results, there are several issues that need to be resolved. In their previous study using the same cohort, they showed a significantly reduced risk of KD from 6 to 30 months of age in those who were exclusively breastfed (odds ratio [OR]: 0.26; 95% confidence interval [CI]: 0.12–0.55) or even partially breastfed (OR: 0.27; 95% CI: 0.13–0.55) compared with those fed formula without colostrum. Thus, breastfeeding markedly reduces the risk of developing KD. However, children born prematurely usually require longer hospitalization and are often separated from their mothers for longer periods of time, missing the opportunity for colostrum and full breastfeeding. Therefore, preterm birth and non-breastfeeding seem to be strong confounders of one another. It could be difficult to conclude that preterm birth has a synergistic risk on non-exclusionary breastfeeding for development of KD.

In their study, a significant causal relationship between gestational weeks and incidence of KD was shown using restricted cubic analysis. However, as the gestational week became earlier, the 95% CI became wider. As a result, as the week of birth became earlier, the statistical reliability became lower. This is because the number of extremely preterm infants who developed KD was very small. Preterm birth may be a risk for KD, but its effect is quite limited. In the real world in Japan, there is a huge gap between the increase in preterm births and the increase in KD. Specifically, preterm births comprised 4.1% of all births in 1980 and increased to 5.6% in 2015, while the number of KD patients was 3932 in 1980 and markedly increased to 16,323 in 2015.

Meanwhile, their focus on the increased risk of KD by non-complete breastfeeding is interesting. In newborns and early infants, exposure to maternal microbiota and breastfeeding play coordinated and pivotal roles in immune system development for not only intestinal immunity but also systemic immunity.[6] Breast milk contains a variety of anti-pathogenic substances including secreted IgA, lactoferrin, defensin, short-chain fatty acids, and microRNAs. Breastfeeding can reduce infectious diseases such as gastrointestinal tract infections, respiratory tract infections, and otitis media in childhood.[7] Breastfeeding may prevent disruption of immune system development by infectious diseases. Furthermore, the benefits of breastfeeding may persist throughout life and reduce the risk of immune-related diseases. Breastfed infants were reported to have reduced risks of celiac disease, type-1 diabetes, and inflammatory bowel disease.[7] These findings suggest that breastfeeding may induce long-term epigenetic modifications in the immune system. In view of these facts, the authors' hypothesis that breastfeeding reduces the risk of KD is understandable.

As the authors discussed, the associations between types of gastrointestinal bacterial flora and risk of KD are interesting topics for research. Recently, an association between systemic inflammation and increased gut permeability was found in a mouse model of KD.[8] Zonulin, a modulator of tight junction permeability between cells in the gut wall, was significantly increased in the KD mouse model. The combination of highly immunogenic bacterial flora and increased gut permeability may be associated with the

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systemic inflammation in KD. Further research is expected in this new field.

Recently, we reported risk factors for KD up to 12 months of age using data from another large-scale prospective birth cohort in Japan, the Japan Environment and Children's Study.[9] We analyzed 90,486 children who were followed for 12 months. Among them, 343 children developed KD. Multivariate logistic regression identified the following risk factors for KD: insufficient intake of folic acid during pregnancy (OR: 1.37; 95% CI: 1.08–1.74), maternal thyroid disease during pregnancy (OR: 2.03; 95% CI: 1.04–3.94), and presence of siblings (OR: 1.33; 95% CI: 1.06–1.67). Unfortunately, the results of the two studies in Japan did not agree.

In our study, we compared full breastfeeding and non-full breastfeeding groups and found a significant difference in the incidence of KD between the two groups. Meanwhile, no significant difference in the incidence of KD was observed between the preterm birth (≤36 weeks) group and the non-preterm birth group. Although our study had a larger sample size, we examined the risk of KD up to 12 months of age, while Takeuchi et al. examined the risk up to 66 months of age. It is possible that these differences in the analyzed populations led to the differences in the results. Currently, we are planning to analyze the risk factors for KD up to 36 months of age and compare the results with those of Takeuchi et al.

It has been 60 years since Dr. Tomisaku Kawasaki encountered the first case of KD in Tokyo, Japan, in the winter of 1961. However, the etiology of KD and the reason for its increasing incidence in many countries remain great medical mysteries in the pediatrics field. Dr. Kawasaki sadly passed away in June 2020. He continued to regularly attend Japanese and International KD Conferences until a few years before his death. He was expecting his research to: (i) elucidate the true etiology of KD, (ii) establish preventive methods, and (iii) develop reliable diagnostic methods. Dr. Kawasaki's wishes have now been handed down to us as a large mission to complete.

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AUTHOR CONTRIBUTIONS

S.I. and S.F. conceptualized and collaborated on the submitted manuscript. T.K. approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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