

Can Breastfeeding in Early Life Protect Infants and Children from Kawasaki Disease?

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SUMMARY

This nationwide population-based longitudinal survey in Japan included a total of 37 630 children, who had data on their feeding during infancy. Authors collected information related to infant feeding practices at 6 to 7 months of age, and used responses to questions about hospital admission for Kawasaki disease (KD) during the period from 6 to 30 months of age. Authors conducted a logistic regression analysis controlling for child and maternal factors with formula feeding (without colostrums) as the reference group. A total of 232 hospital admissions were observed. Children who were breastfed exclusively or partially were less likely to be hospitalized for KD compared with those who were formula fed without colostrum; OR for hospitalization 0.26 (95% CI 0.12,0.55) for exclusive breastfeeding and OR 0.27 (95% CI 0.13,0.55) for partial breastfeeding. Although the risk reduction was not statistically significant, feeding only colostrum also provided a protective effect. The authors observed protective effects of breastfeeding on the development of KD during the period from 6 to 30 months of age in the country in which KD is most common.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Kawasaki disease (KD) is an acute, self-limiting condition mainly affecting infants and young children. However, it has the potential for dangerous cardiovascular complications. It is reported to be the most frequent pediatric systemic vasculitis globally, and the most important cause of acquired heart disease among children. Overall, the highest incidence occurs in Japan and South Korea [1], but several developed and developing countries including India [2-5] are increasingly recognizing this condition. Meticulous records from Japan and Korea show that the incidence is rising progressively, with Japan recording doubling of incidence rate over the past 10-15 years [6-8]. Despite

extensive research, the precise etiology of KD remains unknown. Therefore various angles have been explored and multiple pathophysiologic mechanisms have been suggested. These include infection (bacterial or viral), genetic susceptibility, and autoimmune factors. Proponents of an infectious basis for KD gain support from the coincident age with childhood infections, seasonality, temporal periodicity, self-limiting nature of the condition, and occasional epidemic patterns [9]. However, despite considerable effort, no organism has been implicated with certainty. Genetic susceptibility has been proposed based on occurrence within specific ethnic groups and families [10]. An impressive number of candidate genes is being explored but no definite causative defect has been identified [1]. Immunopathogenetic mechanisms have been proposed based on identification of cytokine/chemokine markers related to immune cells [11]. However none of these theories can irrefutably explain the basis of KD.

The diverse etio-pathogenetic hypotheses reflect the uncertainty in attributing a precise cause-and-effect relationship. Therefore literature is replete with multiple factors considered as associations of KD. Against this backdrop, the recent publication by Yorifuji, *et al.* [12] exploring the association with feeding patterns in early infancy, is instructive. The analysis is robust with multiple statistical adjustments for confounding factors, and also sensitivity analyses for plausible contributing factors.

Critical appraisal: Overall, this was a well-designed and well-conducted study with several strengths. The study was designed to enroll a cohort of infants, representing the birth cohort of Japan, who were followed till 2.5 years of age. The investigators obtained a very high response rate (almost 90%) to the initial questionnaire about feeding practices. As expected, there were dropouts at the time of subsequent questionnaires, but the authors accounted for this, and presented comparative baseline data of the entire cohort – those with missing data and

those who could be included in the analysis. There were no apparent clinically significant differences with respect to gender, gestation, birth order, or singleton status (although some minor variations did achieve statistical significance). However, infants whose data were unavailable for outcome analysis had significant maternal differences with regard to age, smoking status, educational level, and residential area. More important, there were statistically significant differences in the proportion of breastfed and formula fed infants in the two groups. However, this could not be explored further.

The investigators undertook multiple analyses to adjust for potential confounders. They used two additional models, first to control for infant related factors, and another to adjust for maternal plus infant factors. It is significant to note that the results were robust and comparable across all three models. The investigators also explored the relationship of the outcome (occurrence of KD) after adjusting for day-care center exposure, family income, type of residence, etc. They also re-analyzed the results to see if providing colostrum at birth followed by subsequent formula feeding had similar effects as breastfeeding. They observed some benefit although it did not achieve statistical significance. Among the partially breastfed infants, longer duration of breastfeeding did not appear to significantly increase the 'protective effect'.

One of the merits of this publication is that the authors have interpreted the results cautiously despite observing statistically and clinically meaningful differences in the occurrence of KD between those who were breastfed *versus* formula fed. They emphasized that their observations indicate a 'protective association', rather than actual protection. This is valid considering that this is the first study exploring this association, and also because breastfeeding has various specific as well as non-specific health benefits. The investigators themselves observed an overall reduction in all-cause hospitalization among breastfed babies. Considering that the 'protective benefit' was observed even with partial breastfeeding and potentially also with just the consumption of colostrum, this caution is justified. On the other hand, it is possible that the protective association is related to one or more factors available in colostrum and/or the initial breastmilk, rather than breastfeeding *per se*. This requires further exploration and was perhaps outside the scope of this study. Its importance lies in the fact that if such a factor(s) could be identified, it may be possible to provide this to infants at birth or early life even if breastfeeding is not feasible.

The investigators recognized some limitations in their

study including their inability to correlate self-reported hospitalization for KD with actual hospital records. It could be argued that this may be a significant lacuna in a country where electronic records and nation-wide databases are available. However, the authors attempted to correlate the number of infants identified in this study, with national level surveillance data and found comparable results. This is important because significant deviations could reflect inaccurate reporting by parents. \Could the investigators have done more to enhance this study? The accuracy of parental reporting of feeding patterns in early infancy, as well as information on KD hospitalization, is assumed but not proven. Of course since KD is a well-known condition in Japan, and almost 70% mothers were educated beyond high school level, it is expected that the information provided could be reasonably accurate. One simple way to confirm the accuracy would have been to independently cross-check the information available from the questionnaires, in a random sample representing the full cohort.

The investigators built their cohort by enrolling all infants born within a two-week period during the month of May 2010. This means that outcome reporting at 18 months covered one full winter season and two summer seasons. Thus the enrolled infants were approximately six-month-old at the onset of the first winter season. KD epidemiology is well recognized to be influenced by seasonality and climatic conditions [13-15], with higher incidence during winter and lower during summer [6]. Although rare(r), KD has been reported in young infants and even neonates [16]. For these reasons, it would have been ideal to build the cohort by enrolling infants throughout the year, rather than 14 consecutive days in early summer.

KD has been reported to occur among twins-monozygotic as well as dizygotic [17-20]. Twins provide an excellent opportunity to explore KD as they share genetic material, nurture patterns, as well as environmental conditions. In this study [12], only 7 (of 232) infants hospitalized for KD were twins. Although the number is small, it would be worthwhile to learn whether any of these 7 included both twins. Perhaps more important, KD occurs in families also [1]. In this study [12], over 60% of the infants with KD had older siblings. As a separate analysis, if the survey had included questions about KD in siblings during the same time frame as the index infants, some additional information would have been available.

Finally, it should be remembered that this study [12] pertains to hospitalization for KD, and not all forms of the condition. Given that it is a self-limited disease, many

cases would not be included in this analysis. Whether the protective association with breastfeeding would hold good for all forms of KD remains to be explored.

Extendibility: There is no data from anywhere in the world to directly compare the results of this study. On the one hand, it suggests a beneficial effect of breastfeeding; but on the other hand, the effect is possibly non-specific. Overall, it is in sync with the emphasis on immediate and exclusive breastfeeding of newborns and infants. In that context, the results are extendible to the Indian situation. However, data are limited to determine whether exclusive breastfeeding may reduce the incidence of KD in India.

Conclusion: This study suggests that unidentified factors in breastmilk (and that too initial output) may be associated with lower odds of hospitalization with KD later in infancy. This 'benefit' appears to be a non-specific effect rather than specific for KD.

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Neonatologist's Viewpoint

Neonatal Kawasaki Disease, even though very rare, has been reported from different parts of the world [1]. The same is not uncommonly seen in India, ranging from the classical, atypical to the coronary sequelae [2]. As the commonest age of presentation is beyond 6 months of age [3], the neonatologists seldom encounter these cases.

This study has put forward a strong biological plausibility for the role of the breast milk in prevention of the occurrence of Kawasaki Disease (KD). The fact that, there is a reduction of the occurrence of the KD in babies who have been fed the breast milk even for the 3-4 months' period reaffirms the role of defective immune-modulation in the causation of the KD [4].

The study was based solely on the questionnaire and there was no reconfirmation by the telemedicine photograph transfers or a physician's examination. This might have missed few cases, especially more of the younger KD, as it has been seen that the KD has an atypical presentation in the younger age group. The

neonatal diagnoses and the admissions were not captured, as the KD was not an outcome in the first 6 months of age and not included in the questionnaire [4].

Hence for a neonatologist, the study may not add much to the knowledge base of presentation and management of the KD in the neonatal period, but is a strong message that ensuring the breastfeeding in the initial 4 months of age, has wide benefits; some beyond the current understanding.

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