Asian Journal of Pediatric Research

Volume 14, Issue 10, Page 22-28, 2024; Article no.AJPR.124166
ISSN: 2582-2950

The Link between Dengue Fever and Kawasaki Disease in Children

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i10392

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/124166

Minireview Article

Received: 03/08/2024
Accepted: 07/10/2024
Published: 09/10/2024

ABSTRACT

The association between Kawasaki disease and dengue fever is uncommon and can be difficult to diagnose due to overlapping clinical symptoms. There have been few reported cases of children with confirmed dengue fever developing Kawasaki disease. A prior infection of dengue fever pronouncing a worse manifestation of Kawasaki disease is due to the very rare cases of this entity unknown. If a prior dengue fever associated with later Kawasaki disease leads to higher incidence of coronary dilatations in children are not clearly ruled out. The population of this concomitant entity is very small and therefore difficult to analyze incidentally due to high significant scientific standards. What is known is, that differentiating both diseases shows sometimes a clinical dilemma in children.

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Cite as: *Bittmann, Stefan, Elisabeth Luchter, Lara Bittmann, and Elena Moschüring-Alieva. 2024. "The Link Between Dengue Fever and Kawasaki Disease in Children". Asian Journal of Pediatric Research 14 (10):22-28. https://doi.org/10.9734/ajpr/2024/v14i10392.*

Keywords: Dengue; kawasaki disease; risk factor; children.

1. INTRODUCTION

Dengue fever, also known as breakbone fever, is a disease caused by infection with the dengue virus. The virus is a 40 to 60 nm enveloped RNA virus with positive polarity from the Flavivirus family. It is transmitted through the bite of a mosquito and is prevalent in tropical and subtropical regions. The only known hosts of the virus are primates and various mosquito species. There are four different serotypes of the virus, which likely jumped from primates to humans independently in Asia over the past 2000 years. Since World War II and globalization, dengue fever has been on the rise due to the spread of its vector and is often referred to as an emerging disease. Dengue fever is the fastest-spreading viral mosquito-borne disease, with cases increasing thirtyfold from 1960 to 2010. The disease often presents with nonspecific symptoms resembling severe flu, but it can also lead to internal bleeding. In severe cases, it can result in hemorrhagic dengue fever or dengue shock syndrome, both of which can be fatal. The World Health Organization estimates that annually 50 to 100 million people get infected, 500,000 experience severe illness, and 22,000 die from dengue fever, with most fatalities occurring in children. Scientists reported in April 2013 in the journal Nature that their research indicated around 390 million people are actually infected with the dengue virus each year. In Germany, Austria, and Switzerland, there is a mandatory reporting requirement for suspected cases, illness, death, direct and indirect detection of the pathogen, or hemorrhagic disease progression. The exact cause of Kawasaki disease is unknown, but it is believed that infection may be a significant trigger in individuals with a genetic predisposition. Various infectious agents such as viruses, bacteria, rickettsiae, and toxins have been suggested as potential triggers.

The most important vectors transmitting dengue viruses are *A. aegypti* and *A. albopictus* [1-27]. In addition, *A. polynesiensis* and other members of the subgenus *Stegomyia* is associated with dengue in restricted geographical areas [2,3]. *A. albopictus*, which adapts well to cold climate and survives year round, is endemic in China, US and Japan, whereas both *A. aegypti* and *A. albopictus* are present in South-East Asia, including Taiwan [4,6,7]. *A. aegypti* infected with dengue viruses may temporarily be transported by air or ship into Japan and the US and survive during the summer, with the possibility of domestic transmission by *A. albopictus*. These mosquitoes normally feed on a single vertebrate host, but a small percentage of each of the 2 species feed on more than 1 host during 1 gonotrophic cycle and that multiple-feeding behavior is of epidemiological significance. Despite the fact that the vectors can travel up to 2.5 km daily in an open environment, a study in Africa found that only 0.7% of mosquitoes visited more than 4 houses. In contrast, *A. albopictus* is exophilic, an outdoor habitat [1,4,6,7]. These dengue vectors may potentially cause epidemics of DHF/DSS in Japan and the US, and possibly carry the causative agent of Kawasaki disease. The seasonal distribution of Kawasaki disease cases in winter and spring in the USA and Japan, together with the results from a recent study by Burns et al., may be partly explained by the changing habitat pattern of *A. albopictus* from exophilic to endophilic for survival during periods of low temperature and therefore spreading the possible infective agents responsible for KD. Since the 1990s, DF has been a notifiable communicable disease. Local outbreaks have increased due to rising imported cases from global Dengue fever epidemics and China's growing role in international trade. The geographic spread of Dengue fever in China has expanded from southern regions to northern inland areas. Factors influencing Dengue fever spread include dengue virus, mosquito vectors, susceptible populations, environmental conditions, and socioeconomic status. Environmental factors like climate and vegetation affect virus activity and mosquito behavior, while socioeconomic factors like population density and mobility influence human-mosquito contact. The transmission and prevalence of Dengue fever involve complex geo-ecological processes. Dengue fever (DF) epidemics in China are mainly caused by imported cases from natural foci worldwide. Overall, there were more then 320 DF epidemics documented in China. The first reported DF outbreak in China occurred in 1978 in Foshan, Guangdong Province, after a period of no reported cases between 1949 and 1978. Right in that time period, starting 1978, an epidemic of Kawasaki disease was found in Japan. Following the aerosol hypothesis, Dengue fever viral infection could be, hypothetically, a wind-borne trigger of Kawasaki disease from Eastern China to Japan.

2. ASIAN TIGER MOSQUITO (*Aedes albopictus*)

The Asian tiger mosquito is known for biting in forests during the day, earning it the nickname "forest day mosquito" [1-27]. Activity peaks vary by region and biotype, but they typically rest in the morning and at night. They seek hosts both indoors and outdoors, with a preference for outdoor activity. The amount of blood they consume depends on their size. While their bites are not usually painful, they are more noticeable compared to other mosquito species. Tiger mosquitoes tend to bite a human host multiple times if given the opportunity. Ae. albopictus also feeds on mammals and birds besides humans. The females are persistent in seeking a host and are cautious during their blood meal acquisition. They often interrupt their blood meal before obtaining enough for egg development, leading them to bite multiple hosts during their egg development cycle, making them efficient disease transmitters. By biting various host species, the Asian tiger mosquito can potentially act as a bridge vector for pathogens that can cross species boundaries, such as the West Nile virus.

3. Dirofiliaria immitis

Mosquitoes take up infectious larvae, microfilariae, with the blood of infected animals. In the mosquito, they develop into third-stage larvae, which are transmitted to another dog during feeding. In the subcutaneous tissue of the new host, they molt into fourth-stage larvae, which migrate into the bloodstream and settle mainly in the pulmonary artery. In severe infestations, they can *spread to the right side of the heart or even into the vena cava*. There, the larvae develop into adult worms (macrofilariae), which produce new larvae that swim in the bloodstream. Macrofilariae are dioecious, meaning the female parasites give birth to the larvae, which can only develop into infectious third-stage larvae for the dog in the mosquito. Therefore, the number of macrofilariae depends on the number of transmitted third-stage larvae during the mosquito's feeding. To date, there are no pediatric case reported, in which this agent could induce pediatric coronary arterial aneurysm.

4. DISCUSSION

Kawasaki disease (KD) is a systemic vasculitis that primarily affects young children and can lead to coronary artery dilations and aneurysms [1-27]. The exact cause of KD is still unknown, but recent insights from the epidemiology of KD in Japan, where it is most prevalent, suggest a potential infectious trigger [2,8,11,12]. The global changes in KD incidence during the COVID-19 pandemic and a new birth cohort study in Japan also support the theory of person-to-person transmission of an infectious agent. However, the increasing incidence of KD in Japan, with consistent waves nationwide, suggests a more intense exposure that cannot be solely attributed to person-to-person spread. Understanding the cause of KD is crucial for developing accurate diagnostic tests and more effective targeted therapies in the future. Resolving the mystery of KD's etiology remains a key focus in pediatric research.

Dengue fever was first mentioned as far back as the Chinese Jin Dynasty (265–420) and continued to be reported in various regions throughout history. Dengue epidemics occurred in Greece in 1927–1929 and spread globally in the 1990s due to factors such as urbanization and globalization. Dengue is considered an emerging disease and has experienced outbreaks in different countries, with alternating serotypes causing epidemics. Research efforts in the 20th century led to the identification of the dengue virus and the discovery of its transmission by the Aedes aegypti mosquito.

The main vectors of Dengue fever viruses are the females of the yellow fever mosquito, Aedes aegypti, also known as the Egyptian tiger mosquito or dengue mosquito and the Asian tiger mosquito which is also spreading in Europe. Other mosquito species may also serve as vectors for Dengue fever in certain regions, such as the Polynesian tiger mosquito in the southern Pacific or Aedes scutellaris in New Guinea. The Dengue virus is transmitted by female mosquitoes when they feed on the blood of an infected person [14,15]. The virus enters the mosquito's stomach and can infect the stomach epithelial cells if the virus concentration is high enough. From there, the virus enters the mosquito's hemocoel and then the salivary glands. When the mosquito feeds again, it injects its saliva into the wound, transmitting the virus into the bloodstream of the bitten host. There is also evidence of vertical transmission of the Dengue virus from female mosquitoes to their offspring, including larvae. This infection of vectors without a previous blood meal seems to

play a role in maintaining a virus reservoir between outbreaks. There are two epidemiologically distinct infection cycles in which the virus is transmitted from mosquitoes to humans or other primates. The urban cycle involves the yellow fever mosquito and the Asian tiger mosquito, which are well adapted to large urban centers and can transmit Dengue fever and other diseases. In addition to the urban cycle, there is a sylvatic cycle in Africa and Asia, but likely not in America, where mosquitoes such as Aedes furcifer and Aedes luteocephala serve as vectors. In the jungle, mainly non-human primates are infected. While only DENV-2 circulates sylvatically in Africa, it is likely that all four serotypes circulate sylvatically in Asia. There is no evidence that the sylvatic cycle has been involved in past Dengue epidemics, but it is known that the pathogens of the sylvatic cycle can also infect humans. Dengue fever is endemic in tropical and subtropical regions, with 75% of global Dengue cases occurring in the Asia/Pacific region. Major endemic areas include Latin America, Central Africa, India, Southeast Asia, parts of the Pacific (including New Caledonia and Hawaii), and the southern United States. Approximately half of the world's population lives in endemic areas, with WHO estimates of 50 to 100 million cases, 500,000 severe cases, and 22,000 deaths annually. In Asia, over 90% of severe cases occur in children [1-25]. The number of cases doubled from 2000 to 2010, with Laos and the Philippines particularly affected. Guatemala declared a health emergency in early September 2023 due to at least 22 deaths and over 12,000 reported infections since January 2023. In Europe, Dengue is not endemic, but with the spread of vector mosquitoes Aedes aegypti and especially Ae. albopictus, the risk of locally transmitted infections originating from imported cases is increasing. An outbreak of Dengue occurred on the Portuguese atlantic island of Madeira between September 2012 and March 2013, with 1,080 confirmed cases. The vector mosquito was Aedes aegypti, introduced to the island in 2005. The Asian tiger mosquito Aedes albopictus is now widespread in Southern Europe and expanding its range. The first autochthonous cases of Dengue fever occurred in Southern France and Croatia in 2010. In August 2015, two locally acquired Dengue cases were reported in Nîmes, Southern France. In October 2018, five more locally acquired cases were reported in Saint-Laurent-du-Var. The first locally acquired cases in Italy were reported in 2020 in the Veneto region. From 2019 to September 2023, 116 autochthonous Dengue cases were reported in the EU/European Economic Area (EEA), with France having the highest number of cases. In August 2023, seven locally acquired infections were reported on the western shore of Lake Garda. In Switzerland, the number of registered Dengue cases increased tenfold in 2023 due to the resumption of travel after the COVID-19 pandemic, with all infections occurring during foreign vacations. Dengue is transmitted by a mosquito bite and has an incubation period of 3 to 14 days. 80% of infections are asymptomatic, while the remaining 20% present with mild to moderate symptoms. Severe cases are rare and usually occur after a second infection. Symptoms include fever (up to 40 °C) with chills, severe headache, muscle and joint pain, and a rash. Late manifestations may include diffuse hair loss up to two months after the onset of the disease. The disease typically resolves within 3 to 7 days for most patients. In 2 to 4% of cases, severe Dengue fever or Dengue shock syndrome occurs, with a mortality rate of 1 to 5%, reaching up to 15% in some epidemics. During infection with one of the four Dengue serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), antibodies are produced against that specific serotype, leaving the individual vulnerable to viruses of other serotypes during a second infection. In a second infection with a different serotype, antibodies from the first serotype cannot neutralize the new virions, leading to enhanced infection. This phenomenon, known as antibody-dependent enhancement (ADE), can result in a higher viral load and more severe symptoms. Children are particularly susceptible to severe Dengue fever due to declining maternal antibody levels. The ADE hypothesis is supported by epidemiological data, such as the Dengue epidemics in Cuba caused by different serotypes over time. The origin of the name dengue is not definitively clear. It was initially referred to as dandy fever, and later the Spanish term dengue emerged, indicating a distinctive change in posture and behavior in affected individuals. Some sources suggest that dengue comes from the African language and refers to a seizure caused by an evil spirit. Various studies have been conducted to develop a safe Dengue virus vaccine, with ongoing research on potential treatments and preventive measures. A promising compound called JNJ-A07 has shown effectiveness in combating the Dengue virus and could be a potential treatment option in the future. Further studies are needed before its practical application.

It has been observed that children can develop Kawasaki Disease following a dengue fever infection. *Only few cases are reported in this association to date* [1-27]. Also, a few cases of Dengue fever with multiple inflammatory syndrome in children were described [20,23].

The potential link between Kawasaki Disease and Dengue is intriguing. Jagadeesh et al. suggested the need for prospective studies to investigate whether dengue could be a causative factor for KD [21]. Researchers observed that their patient did not exhibit abnormal platelet levels, possibly due to the simultaneous presence of KD and dengue [21]. It has been reported that many KD patients show serological evidence of dengue infection [21]. The co-occurrence of these two conditions can pose diagnostic challenges. If dengue indeed induced KD in this instance, there should have been distinct phases of immunological dysregulation, and the balance between platelet levels should not have been disrupted.

There could be a *large number of unreported cases*, whereby symptomatic children not being tested for dengue fever. It should be recommended to test all Kawasaki patients for Dengue infection. Depending on the country, this is not common practice in clinics. Further research should focus on all these few rare cases in Thailand, India and Brazil, which are to date a very rare population of a tropical virus acting as a trigger for a severe disease in childhood leading to myocarditis, coronary aneurysm and rarely death of young children below age 5.

5. CONCLUSION

Kawasaki disease is a febrile, acute, and self-limiting form of vasculitis that primarily affects medium-sized arteries, particularly the coronary arteries. Why the coronary vessels are the primary target organ in Kawasaki disease, is not well understood. It is commonly seen in children under the age of five, untreated leading to myocarditis, coronary dilatations and rarely death. The exact cause of Kawasaki disease is still unknown, but it is believed that various infectious agents may trigger its development in individuals with a genetic predisposition. Many characteristics of Kawasaki disease resemble those of *viral infections* like influenza, Epstein-Barr virus, adenovirus, and, as seen in our report and the few references to date, *tropical infections such as Dengue Virus.* Children with Kawasaki disease should be tested for Dengue in any instance.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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