

## Kawasaki Syndrome in Germany: Historical Aspects and Current Update

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### Introduction with Historical Aspects

Through his analytical powers of observation, the Japanese physician Kawasaki became aware of a rare childhood disease that his colleagues mistook for scarlet fever. Even more than five decades later, there is only conjecture as to the cause, despite intensive research. Kawasaki syndrome even made it into the American blockbuster medical series Dr. House. For the Japanese pediatrician Tomisaku Kawasaki, who was regarded as very modest, it must have come as a great surprise when his name became established in medical circles worldwide at the end of the 1970s as the term for the acute inflammatory disease of the blood vessels in young children that he discovered [1].

Kawasaki had fought clear-sightedly and extremely tenaciously for many years against the resistance of his colleagues in Japan to have this unusual childhood disease recognized (see box): "I had never seen such a combination of symptoms before, nor was it to be found in any medical textbook," he later recalled of his first small patient with this disease (1). At that time, after all, he already had eleven years of experience as a pediatrician in a hospital. At an internal conference, his colleagues suspected a case of scarlet fever, but Kawasaki thought this was not true. They agreed on an "undetermined

diagnosis." For a long time, even the doctors at his clinic did not want to accept that he had discovered a new disease. Kawasaki continued to research. When another child was admitted a year later with similar symptoms, he was convinced that it must be a new "mysterious disease." In 1967, after six years of studying the serious childhood condition, he was finally able to present his findings on the disease, which he called "acute febrile mucocutaneous lymph node syndrome," in a Japanese journal based on 50 patient cases. His 44-page study met with a lively response from the Japanese medical

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community, especially since there had been sudden deaths of infants in the meantime in which Kawasaki's discovery was suspected to be the cause. Tomisaku Kawasaki was born on February 7, 1925, the last of seven children into a poor family in Tokyo. He became passionately interested in botany as a youth, but - following his mother's wishes - took up medical studies at Chiba State University shortly after the end of World War II. After graduation and several unpaid practical stations, he felt what he was called to do: "While adult patients are always complaining, sick children say very little. I just really liked children." Through a recommendation, Kawasaki obtained a position as a pediatrician at the Red Cross Hospital in the Hiroo district of Tokyo - a position he would hold for more than four decades. After his retirement, he became director of the newly established "Japan Kawasaki Disease Research Center." He was awarded prizes in Japan and worldwide and also taught in the USA. In Japan, Kawasaki syndrome affects approximately 265 out of every 100,000 children under the age of five, and five to eight in Europe and the United States. In Germany, per year, only 300 cases of Kawasaki Syndrome were found and treated in hospital. If left untreated, the disease can lead to irreversible damage to the coronary vessels with a fatal outcome. It is to Kawasaki's credit that his precise description of the clinical symptoms made early diagnosis possible and thus decisively improved the chances of cure. In 1979, Kawasaki syndrome was included in the 11th edition of the "Nelson Textbook of Pediatrics" - the standard US pediatric textbook - and was thus established as a term internationally. In 1961, Tomisaku Kawasaki had treated a

four-year-old boy whose fever, swollen lymph nodes, raspberry tongue, and whole-body exanthema did not respond to antibiotics. He suspected a previously unknown disease, which he later realized was associated with vasculitis and could lead to life-threatening cardiac complications. In 1967, he published his findings based on 50 patient cases in his native language, and in 1974 also in English. The cause of the disease, which affects young children mainly in Asia, and less frequently in Europe and the USA, is still unclear. In addition to genetic factors, infectious triggers and environmental aspects such as heavy metals and mycotoxins are discussed. Kawasaki died on 5th of June 2020 in Tokio with the age of 95 years. After him, the Japan Kawasaki Research Center was named and founded.

### **The Syndrome**

Kawasaki syndrome concludes a group of children who had fever, rash, bilateral conjunctivitis, enanthema, swollen hands and feet, ptosis and enlarged lymph nodes in the neck. Initially, the condition was referred to as "mucocutaneous lymph node syndrome". Cardiac complications such as aneurysms of the heart arteries were also reported. In general, Kawasaki syndrome (KD) is an acute systemic vasculitis, there is inflammation of the blood vessel walls, which can lead to bulging aneurysms in any medium-sized artery in the body, especially in the coronary arteries. However, most children experience only the acute symptoms of general disease without cardiac complications. Kawasaki syndrome, although a rare disease, is one of the most common vasculitides in children, along with Purpura Schönlein-Henoch. Kawasaki syndrome occurs

throughout the world, but is most common in Japan. Incomplete and complete cases of Kawasaki syndrome were described. It is a disease that occurs almost exclusively in young children. Approximately 85% of children with Kawasaki syndrome are younger than five years old, with a peak incidence between 18 - 24 months of age. Patients younger than 3 months or older than 5 years are less common, but are at higher risk for coronary artery aneurysms. The condition is more common in boys than girls. Although Kawasaki syndrome can be diagnosed at any time during the year, seasonal clusters may occur, meaning more new cases occur in winter and spring. In Germany, only 300 cases of Kawasaki disease were hospitalized and treated at hospital, supposing the low prevalence of the disease in Germany compared to countries like Japan or China. The cause of Kawasaki syndrome remains unclear. Some features suggest that an infection precedes the onset of the disease. Hypersensitivity or a misdirected immune response triggered by an infectious agent or its components may progress to an inflammatory process that can lead to inflammation or damage to blood vessels in certain individuals with the appropriate genetic predisposition. Moreover, superantigens could play a major role in Kawasaki disease [1]. Kawasaki syndrome is not a hereditary disease, although a genetic predisposition is suspected. It is very rare for more than one family member to have Kawasaki syndrome. The disease is not contagious and is not transmitted from child to child. Currently, there is no known screening or prevention. It is possible, although rare, for a patient to develop a second episode of the disease. The disease is manifested by high fever for which there is no

explanation. The child usually exhibits high irritability. Nonpurulent conjunctivitis may accompany or follow the fever. The child may develop various types of rash, such as rash due to measles or scarlet fever, urticaria, papules, etc. The rash mainly affects the trunk and limbs and often the diaper area, causing redness and scaly skin. Typical changes in the mouth include highly red, cracked lips, a red tongue, and a reddened throat. Symptoms on the hands and feet include swelling and redness of the palms and soles. Fingers and toes may look bloated and swollen. These symptoms are followed by the appearance of scaly skin around the tips of the fingers and toes (around the second to third week). More than half of patients present with enlarged lymph nodes on the neck. In most cases, it is a single lymph node that assumes a size of at least 1.5 cm. It is not uncommon that patients do not show all typical symptoms. Then it is called "incomplete" or "atypical" Kawasaki syndrome like it is discussed in rare cases of COVID-19 disease in children [6]. Sometimes other symptoms occur, such as joint pain or swollen joints, abdominal pain, diarrhea, irritability, or headache. In countries where vaccination with BCG (protection against tuberculosis) is given, younger children have redness around the vaccination scar. Since the disease resembles an infection and is difficult to diagnose, many patients receive antibiotics without any effect. Even without therapy, the acute phase of the disease passes by itself. Nevertheless, the disease should be treated with medication to avoid secondary damage. The most feared complication is dilatation of the coronary arteries. Therefore, when this diagnosis is made, doctors administer immunoglobulins directly into the blood to

reduce the harmful effects of the disease. This therapy quickly improves the condition so that within 1-2 days the child is again free of fever and the risk of secondary damage has been minimized. If patients respond poorly to treatment, additional cortisone or a so-called immunosuppressant (cyclosporin), which suppresses the reactions of the body's own defenses, can be given. In this case, the treatment takes place in the hospital. Acetylsalicylic acid (ASA) is then given for several weeks. If doctors find minor changes in the coronary arteries, the child should continue to take acetylsalicylic acid until an echocardiogram shows that the changes have receded. Children under 11 years of age do not need to limit their physical activities, except for the first 6-8 weeks. Children over 11 years of age may be advised against participation in particularly sweaty sports and contact sports, depending on the findings. Annual check-ups with ECG and echocardiography, if necessary, are performed. After the age of 10, the child undergoes regular so-called stress tests. If major dilatations or narrowed coronary arteries are detected during echocardiography, the child receives long-term therapy with acetylsalicylic acid, or warfarin if necessary. Contact sports are strongly discouraged. The child's condition is monitored with semiannual ECG and echocardiography examinations and annual exercise testing. The disease is benign and self-limiting in the vast majority of cases, but in exceptional cases the syndrome can lead to severe cardiac complications. Without proper therapy, aneurysms occur in 20-25% of cases and myocardial infarctions in 1.2% of cases. With current therapy with immunoglobulins and acetylsalicylic acid,

the percentage of aneurysms is reduced to less than 5%.

### **Kawasaki Syndrome in Germany**

The incidence in Germany, described in a German analysis, corrected for underreporting, was 7.2 of 100,000 in children younger than 5 years in Germany [8]. Underreporting to ESPED was estimated at 37%-44%. Overall, 315 validated Kawasaki disease cases were reported. Of the 64 (20%) incomplete cases, 58% (37/64) were detected through echocardiographic findings and 42% (27/64) through laboratory criteria alone [8]. Incomplete cases were younger than complete cases (1.2 vs. 2.0 years,  $P = 0.0001$ ) and had more coronary aneurysms (43% vs. 11%,  $P = 0.0001$ ) [2]. Based on this German study, a substantial number of incomplete Kawasaki disease cases were diagnosed based on the laboratory and echocardiographic criteria only [8]. This was particularly the case in relation to infants younger than 1 year-an age group known to have an increased risk of developing coronary aneurysms. In addition, we found a high rate of underreporting to national Pediatric Surveillance Units. An improvement surveillance and development of better diagnostic tests remain a high priority [8]. In a German study published by Jakob et al. in 2018, a total of 301 children were eligible for assessment of their response to IVIG treatment [9]. Among those, 177 children were followed-up for 1 year to identify persistent CAA [9]. Although all scores were significantly associated with being refractory to IVIG (relative risk range between 2.32 and 3.73), the prognostic properties were low (likelihood ratio positive: 1.83-4.57; sensitivity in the range

of 0.28-0.53). None of the scores was a significant predictor of CAA 1 year after acute illness. Application of statistical analysis such as Random Forest did not yield a more valid score. The study worked on a valid score to identify high risk Caucasian children, who might need intensive therapy in Kawasaki disease. None of the available scores appears to be appropriate for identifying high-risk Caucasian children with KD who might need intensified therapy [9].

## Conclusion

In conclusion, the incidence of Kawasaki syndrome in Germany based on 300

patients per year is very low. As compared to other countries in Asia like Japan or China or Russia Kawasaki syndrome plays a more important role in national health system [2-6,11]. In Kawasaki disease studies, it was pointed out, that better diagnostic tests are necessary to clearly define Kawasaki disease in German children [9]. In Germany, since the beginning of COVID-19 pandemic, a few cases of Kawasaki-like cases in COVID-19 infected children were described, supposing COVID-19 virus as a trigger for Kawasaki syndrome like features in children [7,12].

## References

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes [in Japanese]. *Arerugi* 1967, 16:178–222.
2. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet*. 2004 Aug 7-13;364(9433):533-44. doi: 10.1016/S0140-6736(04)16814-1. PMID: 15302199.
3. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, et al. American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation*. 2017 Apr 25;135(17):e927-e999. doi: 10.1161/CIR.0000000000000484. Epub 2017 Mar 29. Erratum in: *Circulation*. 2019 Jul 30;140(5):e181-e184. PMID: 28356445.
4. Esterly NB, Wortmann DW. Kawasaki syndrome. *Australas J Dermatol*. 1990;31(2):61-71. doi: 10.1111/j.1440-0960.1990.tb00653.x. PMID: 2095737.
5. Shulman ST, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. *Nat Rev Rheumatol*. 2015 Aug;11(8):475-82. doi: 10.1038/nrrheum.2015.54. Epub 2015 Apr 28. PMID: 25907703.
6. Hicks RV, Melish ME. Kawasaki syndrome. *Pediatr Clin North Am*. 1986 Oct;33(5):1151-75. doi: 10.1016/s0031-3955(16)36113-2. PMID: 3532006.
7. Bittmann S, Weissenstein A, Luchter E, Moschüring-Alieva E, Villalon G. Multisystem inflammatory syndrome in children (MIS-C): The role of viral superantigens in COVID-19 disease. *J Allergy Infect Dis* 2020; 1(1):18-20.
8. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, et al. Kawasaki Disease in Germany, The Pediatric Infectious Disease Journal: February 2016 - Volume 35 - Issue 2 - p 129-134 doi: 10.1097/INF
9. Jakob A, von Kries R, Horstmann J, Hufnagel M, Stiller B, Berner R, et al. Failure to Predict High-risk Kawasaki Disease Patients in a Population-based Study Cohort in Germany. *Pediatr Infect Dis J*. 2018 Sep;37(9):850-855. doi: 10.1097

10. Hameed A, Alshara H, Schleussinger T. Ptosis as a complication of Kawasaki disease. *BMJ Case Rep.* 2017 Jun 9;2017:bcr2017219687. doi: 10.1136/bcr-2017-219687. PMID: 28601797; PMCID: PMC5534803.
11. MD Bakradze, AS Polyakova, V.K. Tatochenko, AA Gusev, VV Chernikov, et al. First Retrospective Analysis of 448 Pediatric Cases of Kawasaki Disease of Two Cohorts from China and Russia . *American Journal of Biomedical Science and Research*, 2020 - 9(3). AJBSR.MS.ID.001384
12. Bittmann S, Weissenstein A, Villalon G, Moschüring-Alieva E, Luchter E. Association of COVID-19 coronavirus and Kawasaki syndrome like features in 1-5 years old children. *The Neuroscience Chronicles, Neurosci Chron* 2020; 1(1):4-5.