East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online)
Published By East African Scholars Publisher, Kenya

Volume-2 | Issue-5| May-2020 | DOI: 10.36349/EASJMS.2020.v02i05.024

OPEN ACCESS

Research Article

Kawasaki Disease: Insights into Symptoms, Signs, Epidemiology, Etiology, Pathology, Complication, Cardiac Manifestation, Diagnosis, and Treatment

Najla Mustafa Asaiah[1], Azab Elsayed Azab*[2], Abduraouf Alamer Mohamed[3]

[1]Department of Pediatric, Sabratha Higher Instiute of Medical Technology, National Board Technical vocational, Libya
[2]Physiology Department, Faculty of Medicine, Sabratha University, Libya
[3]Faculty of Science, Zawia Uuniversity, Libya

Article History
Received: 28.02.2020
Accepted: 12.05.2020
Published: 15.05.2020

Journal homepage:
http://www.easpublisher.com/easms/

Quick Response Code

Abstract: Background**:** Kawasaki disease (KD) is idiopathic autoimmune self-limiting disease. It was discovered by Professor Tomisakan Kawasaki in Japan in 1967. it is the second wide spread vasculitis disease in pediatric. Objectives: The present review is aimed to high light on the symptoms, epidemiology, etiology, pathology, complication, cardiac manifestation, diagnosis, and treatment of Kawasaki disease. It impacts children younger than 5 years old and is common in boys than girls. 85% of children KD younger than 5 years, peak age between 18-24 months. It is considered as common cause of acquired heart disease in children. It is widely spread in developed countries, and it is common in developing countries, such as China, Japan, Korea, and Taiwan. It is remarkable in summer to spring seasons of year particularly in China and Korea, winter and spring seasons in Europe and Australia. It is result from genetic and pathogenic causes by stimulation of immune system extra or over than normal response of body to bacterial or virus antigens. In all KD cases histological appearance like as myocarditis and fibrosis. It is a significant due to cardiac complications such as development of coronary abnormality in 25% of misdiagnosed groups, and 3-5% in resistance groups which treated by Intravenous immunoglobulin (IVIG). Several clinical and laboratory manifestation rise risk of coronary artery abnormality which including fever for long duration, boys, old ages, prolonged increase levels of ESR and CRP, increasing count of white blood cells, normocytic normochromic anemia, hypoalbuminemia, and thrombocytopenia. Cardiac features of Kawasaki disease include heart failure, ECG abrormality, pericarditis, myocarditis, plural effusion, myocardial infarction, valvular incompetence. The purpose of management is decrease inflammation of cardiac cells and cells of coronary artery lining during acute period of illness, and prevent thromybosis formation in coronary artery by intravenous immunoglobulin and aspirin. Conclusion: It can be concluded that KD impacts children younger than 5 years old, peak age between 18-24 months. It is result from genetic and pathogenic, and causes of acquired heart disease in children. KD has a serious cardiac complications.

Keywords: Kawasaki disease, Symptoms, Epidemiology, Etiology, Pathology, Complication,Cardiac Manifestation, Diagnosis, and Treatment.

INTRODUCTION

Kawasaki disease [KD] was first described as mucocutaneous lymph node syndrome [MLNS] (Dajani, A. S. *et al*., 1993; Newburger, J. W. *et al*., 2004). It is idiopathic autoimmune self-limiting disease, but it is considered as parlous disease due to their complications, which mainly based on coronary artery (Burns, J. C. 2009). Also can be defined as a kind of vasculitis and it is the second wide spread vasculitis disease in pediatric (Shulman, S.T. *et al*., 1995). In addition, it is acute unknown origin inflammatory disease influence arterial system mainly medium and small sized arteries of human body (Burns, J.C. & Glode, M. 2004).

History

Kawasaki disease was discovered by Professor Tomisakan Kawasaki in Japan in 1967, and he was provided some information about the symptoms and signs of 50 Japanese children (Kawasaki, T. 1967). In 1968 he introduced the electrocardiogram characterizes of Kawasaki disease patients (Yamamoto, T., & Kimura, J. 1968). Finally in 1972 the physicians confirm the relationship between Kawasaki disease and coronary artery complication (Shigematsu, I. 1972).

Epidemiology

Kawasaki disease impact children younger than 5 years old, it is common in boys than girls by ratio of [1.5:1], around 2% or less of KD patients have recurrence risk (Mason, W. H. *et al*). in addition, it is involve all races (Kato, H. *et al*., 1996). It is remarkable

***Corresponding Author:** Azab Elsayed Azab

in summer to spring seasons of year particularly in China and Korea, winter and spring seasons in Europe and Australia (Burgner, D. & Harnden, A. 2005). It is widely spread in developed countries, and it is common in developing countries, such as China, Japan, Korea, and Taiwan (Huang, W.C. *et al*., 2009). It is considered as common cause of acquired heart disease in children (Sun, J.H. & Zhai, S.B. 2007; Kato, H. *et al*., 1996), 85% of children KD younger than 5 years, peak age between 18-24 months, uncommon KD affect infant younger than 3 months or older than 5 years but if Involved they will be have more risk to coronary artery abnormality (Harnden, A. *et al*., 2002; Gardner-Medwin, J. M. *et al*., 2002; Nakamura, Y. *et al*., 2008; Holman, R. C. *et al*., 2003). Actually is unusual in infants less than 3 months due to draw the passive immunity "antibodies" from their mothers and it is also infrequent in adults due to Natural immunity to different organism has developed (Bell, D. M. *et al*., 1981).

Etiology

Etiology of Kawasaki disease still not completely clear but some researches qualified it is result from two factors: 1] Genetic cause which increase risk of KD in siblings and families suggest a genetic Predisposition (Burgner, D. & Harnden, A. 2005). 2] Pathogenic caused by stimulation of immune system extra or over than normal response of body to bacterial or virus antigens (Pleister, A. & Lekels, D.D. 2003). Some of microorganisms Suspected in relationship between them and Kawasaki disease Like a Parvovirus, Staphylococcus auras, Epstein Barr virus, Chlamydia, Mycobacterium (Nigro, G. *et al*., 1994; Leung, D. Y. *et al*., 1993; Kikuta, H. *et al*., 1993; Normann, E. *et al*., 1999; HSU, Y. H. et a., 1987), corona virus and streptococci super antigens (Dillon, M. J. *et al*., 2010; Yeung, R. S. 2010).

Pathology of KD

The pathology of Kawasaki disease usually impact the genetically susceptible children which elicited by infection agents leading to provisional changes in immune system of the body (Burns, J. C., & Newburger, J. W. 2012; Onouchi, Y. 2012). It is described as activation of in immune system, systemic and non certain vasculitis by inflammation of mucus membrane, blood vessels and lymph nodes (Kim, D.S. 2006), which producing activation of inflammatory cells such as monocytes, platelets, T cells and macrophage. Then these cells agglutinate to endothelial cells which lining the inner side of arteries leads to distraction of inner intimal and external cellular matrix that leads to weakness and dilation of wall of arteries, plus to inflammatory infiltrator damage [Acute phase]. So, in all KID cases histological appearance like as myocarditis and fibrosis (Yutani, C. *et al*., 1981).

Clinical presentation and Complication of KD

The duration of KD about 6-8 weeks and it is characterized by three phases: A. acute Febrile stage. Most of signs and symptoms can be found during it, the first acute Febrile phase which last for 1-2 weeks. B. Sub acute stage which start after finish acute stage, begin to start for 25 days, where is the critical complication occurs, including coronary artery aneurysm CAL. Convalescent stage which start when all clinical presentation of signs and symptoms disappear, and children become normal after 1-2 months (Newburger, J. W. *et al*., 2004). KD diagnosed by combination of clinical criteria and laboratory findings (Diagnostic guidelines for Kawasaki disease). it is depends on presence of fever more than 5 days plus to other temporary obligatory signs, rarely appear together all time of first observation but can appear subsequently (Vierucci, F. *et al*., 2013). Clinical presentations different according to the age, there are not special presentation in infants younger than 1 year (Song, D. *et al*., 2009). The clinical criteria in acute phase is fever usually remitting or hectic higher than 39C° persisting for live or more days and not response to antibiotic or anti-Pyretic therapy (including lever start again before the fifth day in response to medications) (34. Special Writing Group of the Committee on Rheumatic Fever), Bilateral not purulent conjunctivitis, changes in lips including erythema, cracking and fissuring with strawberry longue and redness, diffuse Injection in mucus membrane of mouth and pharynx. polymorphous skin rash [without vesicles or crusts] which considered the most clinical character of KD in acute phase (Newburger, J. W. *et al*., 2004; Lang, B. 2001). redness, in durative edema in palms and soles [acute stage] followed by desquamation of skin membranous from fingertips and perineal desquamation stage (Friter, B. S., & Lucky, A. W. 1988). And uncommon in KD cervical lymphadenopathy usually non purulent, unilateral, firm Painless and it is diameter bigger than 1.5cm, any cervical adenopathy must he considered in child not cure by medication (Yoskovitch, A. *et al*., 200).In addition, clinical sign can be appearing is erythema und indurations at the Bacillus Calmette Guerin BCG site (Brogan, P. A. *et al*., 2002; Sinha, R., & Balakumar, T. B. C. G. 2005), and after the onset of fever by 1 to 2 months, appearance of transverse deep groove across the nails which called [Beaus lines] (Berard, R. *et al*., 2008).

Cardiac manifestation of KD

Kawasaki disease is a significant due to cardiac complications such as development of coronary abnormality in 25% of misdiagnosed groups, and 3-5% in resistance groups which treated by Intravenous immunoglobulin (IVIG) (Burns, J. C. 2007; 5. Burns, J.C. & Glode, M. 2004). The common form of abnormality is aneurysm or dilation normal diameter of coronary artery in newborn and infants 1-2mm and 4.5-5.0mm in teenager (Oberhoffer, R. *et al*., 1980;

Arjunan, K. *et al*., 1986).which occurs At 6-8 weeks from the attack (Suzuki, A. *et al*., 1990) and there are about 2-3% children die due to untreated coronary abnormality (Brogan, P. A. *et al*., 2002; Newburger, J. W. *et al*., 2004). There other complications during adulthood are myocardial infarction, ischemic heart disease and sudden death if untreated (Hui-Yuen, J. S. *et al*., 2006; Satou, G. M. *et al*., 2007), actually Kawasaki disease cause a range of morbidity due to cardiac and non-cardiac complication (Rowley, A.l. & Shulman, S.T. 1998)(Newburger, J. W. *et al*., 2004). KD can be diagnosed when you found 4 symptoms during attack with coronary artery abnormality [CAA] shown by 2 dimension echocardiograph or coronary angiography but should be eliminate another disease can be cause coronary artery abnormality. Several clinical and laboratory manifestation rise risk of CCA which including: 1) Fever for long duration or recurrence after medication. 2) Boys. 3) Old ages. 4) Prolonged increase levels of ESR and CRP. 5) Increasing count of white blood cells 6] Normocytic normochromic anemia 7) Hypoalbuminemia. 8) Thrombocytopenia (Newburger, J. W. *et al*., 2004; Latino, G. A. *et al*., 2010; Newburger, J.W. 2000). Cardiac features of Kawasaki disease include heart failure, ECG abrormality, pericarditis, myocarditis, plural effusion, myocardial infarction, valvular incomptence (Newburger, J. W.. *et al*., 2004). Keep in your mind when the fever and another symptoms related to acute stage finish and the patient enter in sub acute stage there is a high risk to death that is because of coronary artery abnormality plus to thrombocytosis and hyper-coagulation condition and you found also extra cardiac features as respiratory and gastrointestinal symptoms associated with KD such as: Arthralgia, arthritis, uveitis, pneumonitis, vomiting, diarrhea, abdominal Pain, aseptic meningitis, sterile pyuria, hepatitis, otitis media and hydrops of gall bladder, these makes the diagnosis of Kawasaki disease hard (Shiari, R. 2012; Mason, W.H. & Takahashi, M. 1999).

Incomplete KID and atypical KD

Incomplete KD defined us who have lever more than 5 days but the clinical criteria few or less than four 12 Incomplete KD frequent in infants and children who are more than 9 years of age there is risk of CAA high in this group due to delay of diagnose, and late of TVIG response (Sonobe, T. *et al*., 2007; Chang, F. Y. *et al*., 2006). Atypical KD defined as when the patient has a clinical criterionnot typically associated with KD (Haltel, H.M. 2011) Alternatively, atypical KD that means patient hasfive or more clinical criteria plus other features not commonly seen in KD (Newburger, J. W. *et al*., 2004) When KDclinical criteria`s become atypical or less than 4 none laboratory markers help todiagnose KD including increase level of erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) and increase in level of white blood cells (WBC) mainlyneutrophil, thrombocytosis and can you see normocytic norochromic anernia, andThere is abnormality in liver function test such as increase level of transaminase enzyme,hypoalbuminea and increase level of serum Alfa 1 anti-trypsin and commonly sterile pyuria (Newburger, J.W. 2000; Saket, S. *et al*., 2009), generally KD recurrence less frequent but common with incomplete or atypical KD (Zou, L. X., & Gong, F. Q. 2008)..

Differential diagnosis

- Toxic shock syndrome (streptococcal and staphylococcal).
- Staphylococcal scalded skin syndrome.
- Scarlet fever.
- Infection with enterovirus, adenovirus measles, parvovirus, Epstein-Barr virus and
- Cytomegalovirus.
- Mycoplasma pneumonia.
- Rickettsiae.
- Leptospirosis (Shulman, S.T. *et al*., 1995; Tizard, E. J. 1999)

Treatment of KD

Any case of KD must be hospital admission, exam by consultations and Sub-specialists, echocardiography examination, give a medication and follow-up by Cardiologist of pediatric doctors (Dajani, A. S. *et al*., 1993; Gersony, W.M. 1992).The purpose of management is decrease inflammation of cardiac cells and cells of coronary artery lining during acute period of illness, and prevent thromybosis formation in coronary artery by intravenous immunoglobulin and aspirin (Newburger, J. W. *et al*., 2004). Infusion of intravenous immunoglobulin with ten days is help prevention the occurrence of CAA from 25% to 2-4 (Burgner, D. & Harnden, A. 2005) and to decrease duration of fever. The protocol to cure KD by the stander dose of IVIG is a single dose 2g\kg infused over 12 hour (Kawasaki, T. 1995; Sundel, R.P. & Pelly, RE. 2005; Committee on Rheumatic fever), if delay diagnosed patient came after first 10 days of illness in Sub acute period] in this case its cannot cure the coronary lesion due to subside acute inflammatory reaction, or have not fever do not give him IVIG except patient have continues fever give him IVIG (Singh, S. & Kansra, S. 2005; Singh, S. *et al*., 2005). Some of KD cases do not response to first Jose of IVTG and still have fever even 48 hour of administration of medication, this group around 10% of KD pusesso they need second dose of IVIG If do not response add last third of IVIG or corticosteroid or necrosis factor alpha antagonist (TNF α Antagonist) such as Infliximab (Kawasaki, T. 1995; Sundel, R.P. & Pelly, RE. 2005; Committee on Rheumatic fever). Thigh risk of develop coronary artery lesion in whom have high risk of IVIG resistant (Kobayashi, T. *et al*., 2006;Egami, K. *et al*., 2006; Sano, T. *et al*., 2007). In addition to TVIG the aspirin hardworking as anti-inflammatory and anti-thrombotic effect (Kawasaki, T. 1995; Sundel, R.P. & Pelly, RE. 2005) the dose of aspirin 70-80 mg/kg/day every 6 hours [lower dose used in Japan 30-50

mg/kg/day (Kawasaki, T. 1995). If the fever disappear after 14 days of illness the dose decrease to anti-platelet effect 3-5 mg/kg/day as singly dose for the next weeks.

Vaccination and KD

Do not give live viral vaccination such as measles, mumps and rubella, should be delay after IVIG at least months due to passively acquired antibodies conflict with functional of immunization (Mason, W.H. *et al*.) and second reason, IVIG had role in prohibit replication of live viral vaccination (Siber, G. R. *et al*., 1993; Lingam, S. *et al*., 1986.

CONCLUSION

It can be concluded that KD impacts children younger than 5 years old, peak age between 18-24 months. It is result from genetic and pathogenic, and causes of acquired heart disease in children. KD has a serious cardiac complications. Cardiac features of KD are include heart failure, ECG abrormality, pericarditis, myocarditis, plural effusion, myocardial infarction, valvular incompetence.

REFERENCES

1. Dajani, A. S., Taubert, K. A., Gerber, M. A., Shulman, S. T., Ferrieri, P., Freed, M., ... & Wilson, W. (1993). Diagnosis and therapy of Kawasaki disease in children. *Circulation*, *87*(5), 1776-1780.
2. Newburger, J. W., Takahashi, M., Gerber, M. A., Gewitz, M. H., Tani, L. Y., Burns, J. C., ... & Wilson, W. R. (2004). Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*, *110*(17), 2747-2771.
3. Burns, J. C. (2009). Kawasaki disease update. *The Indian Journal of Pediatrics*, *76*(1), 71-76.
4. Shulman, S.T., Inocencio, I. & Hirsch, R. (1995). Kawasaki disease. Pediatr Clin North Am.,42: 1205-1222.
5. Burns, J.C. & Glode, M. (2004). Kawasaki syndrome. Lancet 364(9433): 533-544.
6. Kawasaki, T. (1967). Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi*, *16*, 178-222.
7. Yamamoto, T., & Kimura, J. (1968). Acute febrile mucocutaneous lymph node syndrome (Kawasaki): subtype of mucocutaneous ocular syndrome of erythema multiforme complicated with carditis. *Shonika Rinsho (Jpn J Pediatr)*, *21*, 336-339.
8. Shigematsu, I. (1972). Epidemiology of mucocutaneous lymph node syndrome. *Nippon Shonika Gakkai Zasshi (J Jpn Pediatr Soc)*, *76*, 695-696.
9. Mason, W. H., Takahashi, M., & Schneider, T. L. Recurrences of Kawasaki syndrome in a large urban cohort in the United States. In *Proceedings of the Fourth International Symposium on Kawasaki Disease. Dallas, Tex, American Heart Association*.
10. Burgner, D. & Harnden, A. (2005). Kawasaki disease: What is the epidemiology telling us about the ctiology? Int J Infect Dis., 9:185-194.
11. Huang, W.C., Huang, L.M., Chang, I.S., Chang, L.Y., Chiang, B.L., Chen, P.J., *et al*. (2009). Epidemiologic features of Kawasaki disease in Taiwan, 2003-2006. Pediatr., 2009; 123(3), 401-405.
12. Sun, J.H. & Zhai, S.B. (2007). Development of Kawasaki disease pathogenesis. J Applied Clin Pediatr., 22: 1037-1040.
13. Kato, H., Sugimura, T., Akagi, T., Sato, N., Hashino, K., Maeno, Y., ... & Yamakawa, R. (1996). Long-term consequences of Kawasaki disease: a 10-to 21-year follow-up study of 594 patients. *Circulation*, *94*(6), 1379-1385.
14. Harnden, A., Alves, B., & Sheikh, A. (2002). Rising incidence of Kawasaki disease in England: analysis of hospital admission data. *Bmj*, *324*(7351), 1424-1425.
15. Gardner-Medwin, J. M., Dolezalova, P., Cummins, C., & Southwood, T. R. (2002). Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *The Lancet*, *360*(9341), 1197-1202.
16. Nakamura, Y., Yashiro, M., Uehara, R., Oki, I., Watanabe, M., & Yanagawa, H. (2008). Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005-2006. *Journal of epidemiology*, *18*(4), 167-172.
17. Holman, R. C., Curns, A. T., Belay, E. D., Steiner, C. A., & Schonberger, L. B. (2003). Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics*, *112*(3), 495-501.
18. Bell, D. M., Brink, E. W., Nitzkin, J. L., Hall, C. B., Wulff, H., Berkowitz, I. D., ... & Anderson, L. J. (1981). Kawasaki syndrome: description of two outbreaks in the United States. *New England Journal of Medicine*, *304*(26), 1568-1575.
19. Pleister, A. & Lekels, D.D. (2003). Cryptie infection and autoimmunity. Autoimmun Rev.,2: 126-132.
20. Nigro, G., Krzysztofiak, A., Porcaro, M. A., Mango, T., Zerbini, M., Gentilomi, G., & Musiani, M. (1994). Active or recent parvovirus B19 infection in children with Kawasaki disease. *The Lancet*, *343*(8908), 1260-1261.
21. Leung, D. Y., Kotzin, B. L., Meissner, H. C., Fulton, R. D., Murray, D. L., & Schlievert, P. M. (1993). Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome. *The Lancet*, *342*(8884), 1385-1388.
22. Kikuta, H., Sakiyama, Y., Matsumoto, S., Hamada, I., Yazaki, M., Iwaki, T., & Nakano, M. (1993). Detection of Epstein-Barr virus DNA in cardiac and aortic tissues from chronic, active Epstein-Barr virus infection associated with Kawasaki disease-like coronary artery aneurysms. *The Journal of pediatrics*, *123*(1), 90-92.
23. Normann, E., Näås, J., Gnarpe, J., Bäckman, H., & Gnarpe, H. (1999). Demonstration of Chlamydia pneumoniae in cardiovascular tissues from children

with Kawasaki disease. *The Pediatric infectious disease journal*, *18*(1), 72-73.
24. HSU, Y. H., WANG, Y. H., HSU, W. Y., & LEE, Y. P. (1987). Kawasaki disease characterized by erythema and induration at the Bacillus Calmette-Guérin and purified protein derivative inoculation sites. *Pediatric infectious disease*, *6*(6), 576-578.
25. Dillon, M. J., Eleftheriou, D., & Brogan, P. A. (2010). Medium-size-vessel vasculitis. *Pediatric Nephrology*, *25*(9), 1641-1652.
26. Yeung, R. S. (2010). Kawasaki disease: update on pathogenesis. *Current opinion in rheumatology*, *22*(5), 551-560.
27. Burns, J. C., & Newburger, J. W. (2012). Genetics insights into the pathogenesis of Kawasaki disease.
28. Onouchi, Y. (2012). Genetics of Kawasaki disease. *Circulation Journal*, CJ-12.
29. Kim, D.S. (2006). Kawasaki disease. Yonsei Med J., *46*: 759-772.
30. Yutani, C., Go, S., Kamiya, T., Hirose, O., Misawa, H., Maeda, H., ... & Onishi, S. (1981). Cardiac biopsy of Kawasaki disease. *Archives of pathology & laboratory medicine*, *105*(9), 470-473.
31. Diagnostic guidelines for Kawasaki disease, 5th ed. Japan Kawasaki Disease Research Committee Tokyo, 2002.
32. Vierucci, F., Tuoni, C., Moscuzza, F., Saggese, G., & Consolini, R. (2013). Erythema multiforme as first sign of incomplete Kawasaki disease. *Italian journal of pediatrics*, *39*(1), 11.
33. Song, D., Yeo, Y., Ha, K., Jang, G., Lee, J., Lee, K., ... & Lee, J. (2009). Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. *European journal of pediatrics*, *168*(11), 1315.
34. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association (1992) Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. JAMA., *268(15)*, 2069–2073.
35. Lang, B. (2001). Recognizing Kawasaki disease. *Paediatrics & child health*, *6*(9), 638-643.
36. Friter, B. S., & Lucky, A. W. (1988). The perineal eruption of Kawasaki syndrome. *Archives of dermatology*, *124*(12), 1805-1810.
37. Yoskovitch, A., Tewfik, T. L., Duffy, C. M., & Moroz, B. (2000). Head and neck manifestations of Kawasaki disease. *International journal of pediatric otorhinolaryngology*, *52*(2), 123-129.
38. Brogan, P. A., Bose, A., Burgner, D., Shingadia, D., Tulloh, R., Michie, C., ... & Dillon, M. J. (2002). Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Archives of disease in childhood*, *86*(4), 286-290.
39. Sinha, R., & Balakumar, T. B. C. G. (2005). BCG reactivation: a useful diagnostic tool even for incomplete Kawasaki disease. *Archives of disease in childhood*, *90*(9), 891-891.
40. Berard, R., Scuccimarri, R., & Chédeville, G. (2008). Leukonychia striata in Kawasaki disease. *The Journal of pediatrics*, *152*(6), 889.
41. Burns, J. C. (2007). The riddle of Kawasaki disease. *New England Journal of Medicine*, *356*(7), 659-661.
42. Oberhoffer, R., Lang, D., & Feilen, K. (1980). The diameter of coronary arteries in infants and children without heart disease. Eur J Pediatr.149: 144-145.
43. Arjunan, K., Daniels, S. R., Meyer, R. A., Schwartz, D. C., Barron, H., & Kaplan, S. (1986). Coronary artery caliber in normal children and patients with Kawasaki disease but without aneurysms: an echocardiographic and angiographic study. *Journal of the American College of Cardiology*, *8*(5), 1119-1124.
44. Suzuki, A., Tizard, E. J., Gooch, V., Dillon, M. J., & Haworth, S. G. (1990). Kawasaki disease: echocardiographic features in 91 cases presenting in the United Kingdom. *Archives of disease in childhood*, *65*(10), 1142-1146.
45. Brogan, P. A., Bose, A., Burgner, D., Shingadia, D., Tulloh, R., Michie, C., ... & Dillon, M. J. (2002). Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Archives of disease in childhood*, *86*(4), 286-290.
46. Hui-Yuen, J. S., Duong, T. T., & Yeung, R. S. (2006). TNF-α is necessary for induction of coronary artery inflammation and aneurysm formation in an animal model of Kawasaki disease. *The Journal of Immunology*, *176*(10), 6294-6301.
47. Satou, G. M., Giamelli, J., & Gewitz, M. H. (2007). Kawasaki disease: diagnosis, management, and long-term implications. *Cardiology in Review*, *15*(4), 163-169.
48. Rowley, A.l. & Shulman, S.T. (1998). Kawasaki syndrome. Clin Microbiol Rev., *11:* 405-414.
49. Latino, G. A., Manlhiot, C., Yeung, R. S., Chahal, N., & McCrindle, B. W. (2010). Macrophage activation syndrome in the acute phase of Kawasaki disease. *Journal of pediatric hematology/oncology*, *32*(7), 527-531.
50. Newburger, J.W. (2000). Kawasaki discase: who is at risk? J Pediatr., 2000: *137(2):* 149-152.
51. Shiari, R. (2012). Neurologic manifestations of childhood rheumatic diseases. *Iranian journal of child neurology*, *6*(4), 1.
52. Mason, W.H. & Takahashi, M. (1999). Kawasaki syndrome. *Clin Infect Dis., 28(2*): 169-185.
53. Sonobe, T., Kiyosawa, N., Tsuchiya, K., Aso, S., Imada, Y., Imai, Y., ... & Yanagawa, H. (2007). Prevalence of coronary artery abnormality in incomplete Kawasaki disease. *Pediatrics International*, *49*(4), 421-426.
54. Chang, F. Y., Hwang, B., Chen, S. J., Lee, P. C., Meng, C. C. L., & Lu, J. H. (2006). Characteristics of Kawasaki disease in infants younger than six months of age. *The Pediatric infectious disease journal*, *25*(3), 241-244.

55. Haltel, H.M. (2011). Kawasaki Disease. In: Marcdante K, Kliegman, RM Jenson HB, Behrman RE, Eds. Nelson Essentials of Pediatrics, 6th ed. Philadelphia*: Saunders Elselvier, pp. 343-345.*
56. Saket, S., Mojtahedzadeh, S., Karimi, A., Shiari, R., & Shirvani, F. (2009). Relationship between electrolyte abnormalities, ESR, CRP and platelet count with severity of Kawasaki disease. *Yafteh*, *11*(3), 5-14.
57. Zou, L. X., & Gong, F. Q. (2008). Clinical features of recurrent Kawasaki disease in 20 children. *Zhongguo dang dai er ke za zhi= Chinese journal of contemporary pediatrics*, *10*(5), 617-619.
58. Shulman, S.T., Inocencio, J. & Hirsch, R. (1995). Kawasaki disease. *Pediatr Clin North Am., 42*: 1205-1222.
59. Tizard, E. J. (1999). Recognition and management of Kawasaki disease. *Current Paediatrics*, *9*(2), 97-101.
60. Gersony, W.M. (1992). Long-term issues in Kawasaki disease. *I Pediatr. 121*: 731-733.
61. Kawasaki, T. (1995). General review and problems in Kawasaki disease. *Japanese heart journal*, *36*(1), 1-12.
62. Sundel, R.P. & Pelly, RE. (2005). Kawasaki disease. In: Cassidy JT, Petly RE, Laxer RM, Lindsley CB. Textbook of Pediatric Rheumatology. 5th Ed. Philadelphia*: Elsevier Saunders, p. 521-538.*
63. Committee on Rheumatic fever, Endocarditis, and Kawasaki Disease of the American Heart Asociation's Council on Cardiovascular Disease in the young. Diagnostic pod lines for Kawasaki disease. (1990). *Am J Dis Child.144:* 1218-1219.
64. Singh, S. & Kansra, S. (2005). Kawasaki Disease. *Natl Med J India, 18:* 20-24.
65. Singh, S., Bansal, A., Gupta, A., Kumar, R. M., & BR, M. (2005). Kawasaki disease. *International heart journal*, *46*(4), 679-689.
66. Kobayashi, T., Inoue, Y., Takeuchi, K., Okada, Y., Tamura, K., Tomomasa, T., ... & Morikawa, A. (2006). Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation*, *113*(22), 2606-2612.
67. Egami, K., Muta, H., Ishii, M., Suda, K., Sugahara, Y., Iemura, M., & Matsuishi, T. (2006). Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *The Journal of pediatrics*, *149*(2), 237-240.
68. Sano, T., Kurotobi, S., Matsuzaki, K., Yamamoto, T., Maki, I., Miki, K., ... & Hara, J. (2007). Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *European journal of pediatrics*, *166*(2), 131-137.
69. Mason, W.H., Schneider, T.L. & Takahashi, M: Duration of passively acquired measles antibusly and response to live virus vaccination following gamma globulin therapy for Kawasaki disease. Proceedings of the Fourth International Symposium on Kawasaki Disease. Dallas, Tex, American Heart Association
70. Siber, G. R., Werner, B. G., Halsey, N. A., Reid, R., Almeido-Hill, J., Garrett, S. C., ... & Santosham, M. (1993). Interference of immune globulin with measles and rubella immunization. *The Journal of pediatrics*, *122*(2), 204-211.
71. Lingam, S., Miller, C. L., Clarke, M., & Pateman, J. (1986). Antibody response and clinical reactions in children given measles vaccine with immunoglobulin. *Br Med J (Clin Res Ed)*, *292*(6527), 1044-1045.