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FEVER INDUCED KAWASAKI DISEASE WITH PLATELET DISORDER.

Pharmacy

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ABSTRACT

Kawasaki disease is an illness that causes inflammation of the blood vessels in the body, which mainly involves medium sized arteries and veins. It is usually categorized by a varied number of symptoms, primarily of which consists of fever and platelet disorders. The latter manifests, in most cases as either thrombocythemia (increased platelet levels) or thrombocytopenia (decreased platelet levels). The incidence of thrombocytopenia is seen to be marked by coronary artery aneurysms. Research has shown that the levels of increased platelets (marked by elevated serum levels of thrombopoeitin during the third phase of Kawasaki disease), however exceeds that of the decreased platelet count. Fever also serves as a concurrent factor in the manifestation of Kawasaki disease as seen in the case study. It involves two case presentations, an 18 month old male child and a 4 year old male child with laboratory findings and results that explains in details, the valid need of the illumination into the basic symptoms presented in this study.

KEYWORDS

Kawasaki disease, Thrombocythemia, Thrombocytopenia, Fever. Coronary artery aneurysm.

INTRODUCTION

Kawasaki disease is a serious febrile ailment characterized by the inflammation of a blood or lymph vessel which leads to cardiovascular disorders and coronary arterial aneurysms. It mostly manifests in infants and children. Research shows that among children affected with Kawasaki disease, 80 percent of them are under age 5. It is highly prevalent in Asian countries as well as America and countries situated in the Pacific Islands. The symptoms associated with Kawasaki disease are divided into 3 main phases. The 1st phase is also called the Acute phase, and it lasts for about 1 to 11 days. It is characterized by high fever, conjunctivitis, swollen lymph nodes, redness in tongue, rash on lips, genitals, chest, etc. The 2nd phase is also called the Sub acute phase and it has a duration of about 12 to 21 days with occurrences such as diarrhea, vomiting, desquamation, jaundice, abdominal pain and joint pain. The 3rd phase which is also referred to as the Convalescent phase and it lasts for roughly 22 to 60 days. This phase is characterized by a notable improvement seen in the patients unless unforeseen complications arise. There is no specific or intricate test available for the diagnosis of Kawasaki disease. It is mostly diagnosed by observing the patient's symptoms and laboratory values. Diagnosing the symptoms means observing the presence of fever for 5 or more days as well as conjunctivitis, rash on the body (usually in the chest, neck, stomach or genitals), enlarged lymph nodes in the neck region, desquamation and swelling or redness in the palms and soles. Laboratory tests employed involve C-reactive protein test, urine test, ESR test, Sodium test, Albumin test, and Stress test. Electrocardiogram and Echocardiography are also employed to denote the heart function as it is usually impaired in Kawasaki disease. Blood tests are initiated to investigate the presence of elevated white blood cells, anemia, high sedimentation rate, low red blood cells, and elevated levels of liver enzymes. However these aren't always observed in the early stages of the disease. Urine tests are also carried out to observe the presence of protein in urine. Stress test is employed to detect the presence of B-type natriuretic peptide (BNP) in the blood which is usually released when the heart is compromised. An echocardiogram is usually done after diagnosis as Kawasaki disease compromises the arteries of the heart, and an electrocardiogram is done to record impulses and detect irregularities in the heart's rhythm which as an indication of Kawasaki disease. Risk factors for Kawasaki disease include factors such as Age (children under 5 years are susceptible to this disease), Gender (males are inadvertently more prone to this disease than females as research has shown), Genetics (a child ultimately possesses the potential to have this disease if either one of the child's parent had it), Ethnicity (children from prevalent areas such as Asia and America are more likely to have this disease). In the early period of the year (first 3 months), across the northern hemisphere, the occurrence of Kawasaki disease is 40 percent more than in the later period of the year. Possible causes of Kawasaki disease include viral or bacterial infections, environmental and genetic factors. Antigens produced by bacteria such as streptococci, staphylococci engage immune responses which gives way to the manifestation of inflamed blood vessels, cardiac impairment and compromised blood vessels. Another notable risk factor is the variation of the ITPKC gene which may lead to increased production of cytokines because of the lessened activity of the T cells which subsequently causes inflammation in cells and tissue impairment. Differential diagnosis with Kawasaki disease involve certain disorders which include Scarlet fever, Toxic shock syndrome and Rocky mountain spotted fever, which is why the hypersensitivity notation is an important diagnostic requirement for Kawasaki disease. Other diagnostic requirements include BCG injection, Myocarditis, Hydrops of gall bladder. Kawasaki disease usually occurs as Incomplete Kawasaki disease (which is observed in children younger than 12 to 24 months, occurs without sufficient diagnostic criteria, hence the name, coronary artery aneurysm may or may not be observed and presents with typical fever). Atypical Kawasaki disease (which presents with symptoms such as meningitis, facial paralysis, seizures, pancreatitis, cholestatic jaundice, renal injury and pneumonia, and it may or may not present with coronary artery aneurysm), or Typical Kawasaki disease (which is usually diagnosed with fever for 5 or more days and may or may not present with coronary artery aneurysm). The type of Kawasaki disease presented in the study falls under the category of Atypical and Incomplete Kawasaki disease.

CASE STUDY

CASE 1; An 18 month old male child was brought into the hospital with a case of fever since 10 days, which is of an intermittent moderate grade and is being temporarily relieved with the administration of antipyretics. He had swelling all over his body, which initially started from his lower limbs and later spread to other parts of his body. He had developed maculopapular rashes which initially started from his chest and later spread to his face and limbs after 2 days, they were present upon his administration into the hospital. The patient is dull and unable to walk and presented these values upon examination. His temperature was 99.6F, pulse rate was 110/minute, respiratory rate was 34/minute, and his blood pressure was found to be 90/80mmHg. His hematological tests produced the following results. HB- 7.2g/dl, WBC- 20200/cumm, ESR- 70mm/hr, Platelet count- 350000cumm, CRP- 27mg/dl, PCV- 25%.

Table 1: Drug therapy/plan proposed for 18 month old patient.

MEDICATION (DOSE/ROA/FREQUENCY)	DURATION
Inj. Ceftriaxone (500mg/IV/BID)	5 days after hospitalization.
Inj. Tramadol (15ml/IV/SOS)	2 days after hospitalization.

Inj. Ranitidine (1cc/IV/BID)	8 days after hospitalization.
Inj. Zofer (1cc/IV/BID)	8 days after hospitalization.
Inj. Doxycyclin (2mg/IV/BID)	5 days after hospitalization.
Syp. P-250mg (3ml/PO/QID)	5 days after hospitalization.
Inj. Zenflox (37ml/IV/BID)	From day 3 to day 4.
Tab Aspirin (150mg/PO/TID)	Started on day 5, continued after discharge.
Inj. IVIg (2gm/IV/OD)	From day 5 to day 6.
Tab. Junior Lanzol (15mg/PO/OD)	From day 5, continued after discharge.
Syp. Digene (2 tablespoon/PO/TID)	Last day, continued after discharge.

Treatment started with the administration of IVIg 2g/Kg and an Aspirin tablet 150mg/PO. Contraindication of IVIg is noted so that the patient treated with it should not be subjected to live vaccination for at least 11 months. Likewise patients who have been vaccinated should not be given 1VIg until a safe period of 11 months. The patient was said to have sepsis and he was treated with cephalosporin antibiotics due to elevated procalcitonin levels. Despite the 48-hour treatment with IV antibiotics, the fever persisted and the patient developed an edema. With the treatment regimen changed to bacterial resistant benzyl penicillin, the fever subsided. Blood tests carried out after two days presented the following results, WBC count was 16000/cubic millilitres, Platelet count was 40000/cubic millilitres, ESR was 89mm/hr, PCV was 22 percent, and the CRP was 22mg/dl. Based on the increase in the ESR and platelet count, as well as the presence of hypoalbuminemia, a 2D echo was carried out which revealed an irregular dilation of the coronary artery. The diameters of the dilated arteries are listed as, 2.58mm for the Left Main Coronary Artery (LMCA), 3.78mm for the Left Anterior Descending Artery (LAD), 2.8mm for the Left Coronary Artery (LCA), and 2.14mm for the Right Coronary Artery (RCA). Based on the symptoms and values presented, this patient was confirmed to be diagnosed with Incomplete Kawasaki disease.

CASE 2; A 4 year old male was admitted into the hospital with a case of fever since 5-6 days with dullness. Antipyretics were subsequently administered to abate the symptoms. Upon physical examination, his temperature was in excess of 102F, pulse rate was 140/min, respiratory rate was 38/min, blood pressure was 90/60mmHg, SpO2 was 98 percent and his weight was 18kg. Further tests showed the HB- 9.0, WBC- 9800/cubic millilitres, Platelet count- 120000/cubic millilitres, ESR- 90mm/hr, PCV- 29%, RBS- 89mg/dl, Serum Albumin- 2.0g/dl, and Serum Creatinine- 0.5mg/dl.

Table 2: Drug therapy/plan proposed for 4 year old patient.

MEDICATION (DOSE/ROA/FREQUENCY)	DURATION
Inj. Mero (SB) (14.4ml+20ml/IV/QID)	Discontinued after discharge.
Inj. Linezolide (90ml/IV/BID)	Discontinued after discharge.
Inj. Rantac (1.8cc/IV/BID)	8 days after hospitalization.
Inj. Zofer (1.8cc/IV/BID)	8 days after hospitalization.
Syp. P-250mg (5ml/PO/TID)	5 days after hospitalization.
T. Aspirin (150mg/PO/QID)	Continued after discharge.
Inj. Pipzo (6.7cc+20ml/NS/IV/QID)	Discontinued before discharge.
Syp. Cetrizine (5ml-5ml/BD)	Continued after discharge.
Inj. IVIg (1g/kg/IV)	Prescribed 6th hourly.

After a few days, the fever subsided, the ESR, and Serum platelet levels were stable and the patient was discharged with a low dose aspirin. Subsequent cardiology follow-up for 6 months was advised due to mild cardiovascular infarctions encountered. A notable fluctuation of the HB, WBC, Platelet count, ESR, PCV, Serum levels was observed over the course of treatment. The enteroscreen test proved negative for the antibodies IgG and IgM, the progen test was negative and the procalcitonin levels were found to be negative (0.16mg/ml). The culture report proved the blood was D1 negative on the first day and D3 negative on the last day. Mesenteric lymphadenitis, and mild hepatomegaly with minimal interloop collection was observed in this case. Cervical lymphadenopathy is regarded as one of the most common diagnostic criteria for Kawasaki disease, The patient was diagnosed primarily with fever and thrombocytopenia which are common symptoms of Kawasaki disease with thrombocytopenia noted to be the less common occurring of the two platelet disorders, the other being, thrombocythemia. This case is diagnosed as Incomplete Kawasaki disease due to the absence of other diagnostic criteria and basic symptoms.

DISCUSSION

Kawasaki disease is notably one of the most common causes of vasculitis in children. Early diagnosis and treatment helps in the prevention of serious cardiac complications and treatment within 10 days of onset proves to be helpful in decreasing the risk of lasting damage and greatly reduce the potential for serious cardiac complications by 20%. The noted drug of choice for Kawasaki disease is intravenous immunoglobulins and aspirin with treatment involving infusions of intravenous immunoglobulins (2g/kg) over 12 hours within 10 days. IVIg reduce the synthesis of antibodies, cytokines causing symptoms of Kawasaki disease by influencing T-cells, thereby reducing the inflammation of blood vessels. It also prevents the occurrence of coronary artery aneurysms by 20%, as well as giant aneurysms (reduces possibility to as low as 1%). A subsequent dose of IVIg should be administered to patients who do not respond to the initial dose within 36 hours of administration. A high dose of aspirin is usually prescribed (100mg/kg/day) to avert the formation of blood clots as the platelet number is exponentially high making it more likely to form a thrombus. The administration of aspirin also helps in the alleviation of fever and inflammation. Cardiac complications are subsequently averted due to the administration of aspirin in low doses (3mg/kg). Coronary arteries problems are also prevented with the administration of low doses of aspirin in children recover within the serious phase of the ailment upon being treated with IV immunoglobulins. Aspirin is notably contraindicated in Herpes Zoster infection or flu. Excessive or prolonged use of aspirin proves to be harmful in the long term as it causes liver and brain complications as seen in Reye's syndrome (dipyridamole is used interchangeably in this case). Flu shots are given consequently with prolonged aspirin use as it decreases the risk of severe brain and liver complications. IV immunoglobulins do not always prove responsive to children with Kawasaki disease (research shows as many as 10% of children). In this case, IV methyl prednisolone as well as TNF-alpha antagonist is often advocated for use. A subsequent infusion of IVIg alone or in combination with a corticosteroid or infliximab is administered in patients with resistance. Steroids in combination with cytotoxic agents such as cyclophosphamide are administered to obviate the progression of aneurysms in patients resistant to IVIg therapy. A full recovery without cardiac complications or arterial aneurysms is a possible outcome for patients with Kawasaki disease if treated properly. Although, research shows that at least 60% of patients develop coronary artery complications during the course of this disease. Relapse has been shown to occur, as seen in about 3% of patients. About 25% of patients emerge with complications which include aneurysms, coronary artery problems, cardiovascular disorders, inflammation, etc, and children may develop coronary changes even after treatment, such as arterial aneurysms as Kawasaki disease affects medium sized arteries. Prospective factors for the possibility of Kawasaki disease include sex (male), platelet count, as seen in thrombocytopenia and thrombocythemia and elevated CRP and albumin values, as well as delayed IVIg administration. Coronary aneurysms are diagnosed using imaging from trans-thoracic echocardiography. Aneurysms are considered depending on their size and number; they are also treated based on these factors, as low dose aspirin is administered for small aneurysms and anticoagulants such as warfarin or heparin are administered for big or multiple aneurysms. Myocardial oxygen demand is usually high, as a result of complications arising from this disease, and beta blockers are administered to combat this issue. Cardiac catheters and stress test are used to detect the size of vessels and heart function, in cases with the presence of giant aneurysms. Coronary bypass grafting and cardiac catheters are used to enhance blood flow in arteries in patients with refractory cardiac complications. Post discharge monitoring should be strictly observed in patients with Kawasaki disease, especially those with coronary abnormalities, for a period that ranges from 2 years to 20 years, depending on the severity or extent of the case presented, in case of relapse or other unforeseen complications.

CONCLUSION

The incidence of a fever that is notably high (<39C/102F), and other symptoms and irregularities in platelet count as well as a host of other laboratory values serves as an important indication in the diagnosis of Kawasaki disease, Research suggests that the atmospheric climate in Asia, correlate with the incidence of Kawasaki disease in some places in North America. It is found that Kawasaki disease patients have high levels of toll-like receptors mRNA and irregularities in interleukin -1-

pathway genes, and this has been questioned as a potential causative factor. Due to the natural protection of the maternal antibodies, the disease is less likely to occur in children less than 3 months of age. These maternal antibodies tend to recycle and the body naturally adjusts to the production by response of its antibodies upon exposure to antigens. The signs and symptoms that occur in Kawasaki disease manifest due to the 'genetic variation' that inhibits the production of antibodies in children with Kawasaki disease. Research states that IgG polymorphism is also suggested to be a predominant factor for the incidence of Kawasaki disease. The broad manifestation of this disease is yet to be fully explored, even though research has produced a lot of factual information regarding its existence and intricacies, a lot of specificities are still unknown and are still being studied such as gene variations and the relationship between adenovirus, rhinovirus, corona virus (HCov-NH) and Kawasaki disease.

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