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SCORING SYSTEM FOR PREDICTING INTRAVENOUS IMMUNOGLOBULIN (IVIG) RESISTANCE WHILE TREATING KAWASAKI DISEASE: A REVIEW

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ABSTRACT

Kawasaki disease (KD) is an acute self-limiting inflammatory disorder, associated with vasculitis, affecting predominantly medium sized arteries, particularly the coronary arteries. This disease predominantly affects children below 5 years old and seen in developed countries. Etiology of this disease is poorly understood but genetic susceptibility has been found in some studies. Coronary artery aneurysm (CAA) is one of the most serious complication of Kawasaki disease. Diagnosis is done clinically based on the guidelines. Intravascular immunoglobulin (IVIG) is considered to be the gold standard of the treatment along with anti-inflammatory like aspirin and steroids as in more serious cases. IVIG relieves acute inflammation and has been shown to reduce the rate of coronary aneurysms from greater than 25% in untreated patients to 1-5% in treated patients. Maximal benefits are seen when IVIG is given within the first 10 days of the illness. When fever is not settled after 36 hours of initiation of IVIG then it is considered as IVIG resistance Kawasaki disease. In such case next dose of IVIG given and other medications may also be given according to severity. This prolongs illness and causing more susceptible to coronary complications. To predict the occurrence of IVIG resistance scoring system has been prepared by Kobayashi, Egami and Sano. These are simple scoring system mostly based on laboratory findings and day of initiation of treatment. With the use of these system we can categorize 'high risk' patient so it will be helpful in managing the illness.

KEYWORDS: Intravenous Immunoglobulin (IVIG) Resistance, Predicting Scoring, Kawasaki Disease.

INTRODUCTION

Kawasaki disease, also known as mucocutaneous lymph node syndrome, is an acute, systemic vasculitis of small- and medium-sized arteries that predominantly affects patients younger than five years. It represents the most prominent cause of acquired coronary artery disease in childhood.[1,2] Kawasaki disease was first described in 1967 in a paper entitled 'Acute febrile mucocutaneous lymph node syndrome: clinical observation of 50 cases' which was published in the Japanese Journal of Allergy in 1967[1] by Tomisaku Kawasaki. Kawasaki saw his first case in 1961 with features currently labelled as symptoms for diagnosis of Kawasaki disease (KD). It is very common vasculitis illness in childhood after Henoch Schönlein purpura in developed countries. It is associated with systemic vasculitis affecting coronary arteries causing coronary artery aneurysm (CAA) in 15-25% untreated patients while 2-3% of untreated cases die as a result of coronary vasculitis.[3-6]

Epidemiology: Kawasaki disease was first identified in Japanese pediatric population but it has been found in children all over the world. Due to its cardiac sequelae it is one of the cause of heart disease in childhood in developed countries. KD is most common in young children, with 85% of cases occurring under 5 years of age. In the US, hospitalization data showed a rate of 24.7 per 100,000 children in the year 2010. By race/ethnicity, Asian/Pacific Islander children less than 5 years of age had the highest KD hospitalization rate in 2010 (50.4 per 100,000) followed by children of black (29.8) and while (22.5) race/ethnicity.[7] The average annual incidence in age group <5, 5-10, 10-15, and 15-20 years was 67.3, 5.75, 0.79, and 0.26 per 100,000.[2] The annual incidence rates were 206.2 and 239.6 per 100,000 children aged 0 to 4 years in 2009 and 2010, respectively; the 2010 rate was the highest ever reported in Japan.[8]

Clinical Features and Diagnosis

Diagnosis of Kawasaki disease is clinical diagnosis. There is no definite diagnostic test at present. Diagnosis is based on major clinical features of Kawasaki disease. Different lab investigations are useful while diagnosing incomplete Kawasaki disease. Two most used diagnostic criteria guidelines are in use; Japan Circulation Society and American Heart Association (AHA) guidelines. Below is the diagnostic criteria of Kawasaki disease prepared by AHA (2004).

Table 1: Diagnostic criteria for Kawasaki Disease: fever must be present, with 4 of the 5 other criteria met.

Criteria	Manifestations
Fever	Present for at least 5 days, typically high spiking and remittent, lasts an average of 10 days when untreated
Conjunctivitis	Bilateral conjunctival injection, typically limbic sparing, non-exudative
Mucosal changes	• Erythema, cracking, peeling of lips • "strawberry tongue" • Diffuse erythema of oral mucosa
Lymphadenopathy	Cervical lymphadenopathy; may be single node >1.5 cm in diameter or several smaller, firm, non-fluctuant nodes bilaterally
Polymorphous rash	Commonly maculopapular, but may be erythrodermic, urticarial, or erythema multiforme like; may show early desquamation in the perineal region as well
Extremity changes	Erythema and induration of hands and/or feet seen in acute phase; periungual desquamation may follow in subacute phase

Others manifestations which are not included in the criteria but often noted include: irritability, gastrointestinal complaints, urethritis, arthritis, arthralgia, aseptic meningitis, uveitis and otitis.[9] When we meet criteria for diagnosis of Kawasaki disease then we can start relevant treatment but sometime we find 4 or less manifestations. The AHA statement also includes use of supportive laboratory testing and echocardiogram in order to detect those patients who do not meet the (full) criteria for KD diagnosis. These patients are considered to have "incomplete KD" and are still at risk for coronary abnormalities.[10] Though lab investigations and echocardiography is not required for diagnosis of KD but it is equally important. Those investigations help determining whether 'incomplete KD' needs medications or not. Lab investigations also are important while using scoring system for predicting IVIG resistance.

Table 2. Supplementary laboratory criteria for incomplete Kawasaki disease.

C-reactive protein ≥3.0 mg/dL and/or erythrocyte sedimentation rate ≥40 mm/h with the following criteria	
1.	albumin 3.0 g/dL
2.	anemia for age
3.	elevation of alanine aminotransferase
4.	platelets after 7d ≥450,000/mm^3
5.	white blood cell count ≥15,000/mm^3
6.	urine ≥10 white blood cells/high-power field
Modified from Newburger et al.[3] If ≥3 supplement criteria are met, intravenous immunoglobulin can be prescribed before performing echocardiography. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IVIG= intravenous immunoglobulin.	

Following the criteria in above table we can diagnose Kawasaki disease and move on to treatment options.

Treatment: After confirming typical or complete Kawasaki disease or incomplete Kawasaki disease which needs treatment, we need to start pharmacological treatment in acute phase to minimize the coronary complications of this disease.

Intravenous Immunoglobulin (IVIG): It has been mainstay treatment for acute phase Kawasaki disease. Treatment with single high dose (2mg/kg) of IVIG is effective in reducing the incidence of CALs.[11-13] The mechanism of IVIG is poorly understood though.

Aspirin: It is simultaneously use along with IVIG while treating Kawasaki disease. It acts as an anti-inflammatory. In North America (80-100mg/kg/day) aspirin is most widely used during the acute phase.[14] In Japan, concern about hepatic toxicity has led to use of moderate-dose (30-50 mg/kg per day) as recommended standard therapy in the acute phase.[15]

Corticosteroid: Corticosteroids are highly potent anti-inflammatory drug. Studies has shown conflicting results when corticosteroids used along with IVIG and IVIG alone treatment. Efficacy of corticosteroid has shown improved results in decreasing coronary complication in Japan.[15] There were not conclusive studies to support this finding, therefore export suggest that until these high-risk scores are successfully defined and tested worldwide, IVIG alone (without the addition of corticosteroid) will remain the gold standard initial treatment of Kawasaki disease outside Japan.[16] Methylprednisolone and prednisolone are the commonly used corticosteroid in Kawasaki disease.

Other medications: Anti-tumor necrosis factor (TNF) alpha agents such as infliximab and etanercept are also used to treat Kawasaki disease. These miscellaneous drugs are usually used when IVIG is not responded well or in case of IVIG resistant. Other medication such as potent immunosuppressive agents (e.g.,

cyclophosphamide or cyclosporine) has also been used in the treatment of Kawasaki disease.

Ivig Resistant Kawasaki Disease

Downie et al.[17] defined intravenous immunoglobulin (IVIG) resistance in patients with Kawasaki disease (KD) as any patient who receives a second dose of IVIG and had a fever (body temperature [BT] >38.0°C) since finishing the first IVIG dose (2 g/kg). Once Kawasaki disease is confirmed IVIG is considered to be the gold standard treatment. It should be given within 10 days of initiation of symptoms to minimize the complications of Kawasaki disease. Aspirin is also given alongside IVIG. Treatment with single high dose (2mg/kg) of IVIG is effective in reducing the incidence of CALs.[11-13] IVIG in given with in the duration of 10-12 hours. The mechanism of IVIG is poorly understood though. IVIG relieves acute inflammation and has been shown to reduce the rate of coronary aneurysms from greater than 25% in untreated patients to 1-5% in treated patients. Maximal benefits are seen when IVIG is given within the first 10 days of the illness. Some controversy exists about the ideal time to begin IVIG, but it is given most often from days 5-7. Among the patients with acute Kawasaki disease treated with intravenous immunoglobulin (IVIG), 10-20 % demonstrate resistance or incomplete effects. Cardiac complication such as the coronary arterial aneurysm is frequent in these patients.[18] Demonstration of resistance or incomplete effect is demonstrated by continuing fever even after 36 hours of initiation of IVIG which is 24 hours of its completion.

Guidelines from the American Heart Association recommend a second dose of IVIG, methylprednisolone, a longer tapering course of prednisolone or prednisone plus IVIG, infliximab, cyclosporine, immunomodulatory monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents, or plasma exchange for patients resistant to IVIG.[19] Echocardiography is useful investigation during these periods to evaluate status of coronary aneurysm.

Scoring System for Predicting Ivig Resistance

Given the numbers of resistance cases and second line treatment for IVIG resistant Kawasaki disease several studies has been done to predict the chances of having resistance to IVIG. Most of the factors and scoring system has been developed to predict resistance. These factors and scoring system are mostly based on laboratory findings. Higher the score, there will be chances of having CAAs more. These scores may help with management to the patient.

Scoring system

Several scoring systems has been developed. Most used systems are prepared by Kobayashi, Egami and Sano. The scoring system is tabulated as under.

Table 3. Scoring system for predicting IVIG resistance.[20]

	EGAMI[21]	KOBAYASHI[22]	SANO[23]
		Na ≤133 (2 points)	Total bilirubin ≥0.9 mg/dl (1 point)
	≤4 days of illness (1 point)	≤ 4 days of illness (2 points)	
	ALT >100 U/L (1 point)	ALT ≥ 100 U/L (1 point)	AST ≥200 U/L (1 point)
	≤300 ×109/L platelets (1 point)	≤300x109/L platelets (1 point)	
	CRP ≥8 mg/dL (1 point)	CRP ≥10 mg/dL (1 point)	CRP ≥7 mg/dL (1 point)
	Age ≤6 months (2 points)	Age ≤12 months (1 month)	
		≥80% neutrophils (2 points)	
High risk	≥3 points	≥5 points	≥2 points
Test performance in Japanese vs non-Japanese			
Japanese			
Sensitivity (%)	78	86	77
Specificity (%)	76	67	86
Non-Japanese cases			
Sensitivity (%)	42	33	40
Specificity (%)	85	87	85

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IVIG, intravenous immunoglobulin.

Above scores showing numbers equal or higher than high risk mark usually denotes patient is 'positive' but being 'negative' doesn't rule out the chances of resistant. Above score is more sensitive and specific to Japanese population. Sensitivity is very low for non-Japanese population. Attempts to develop a more sensitive and specific score for patients outside of Japan have thus far been unsuccessful.[24] Beside above predicting calculator there are some other predicting factors those predict IVIG resistance. Levels of AST and lactate dehydrogenase and percent of neutrophils: patients with abnormal levels of liver markers (AST and lactic dehydrogenase [LDH]) and neutrophils have a high risk for IVIG resistance.[25] N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels and percent of polymorphonuclear neutrophils (PMNs) is also another major predicting factor for IVIG resistance. Patients resistant to IVIG have significantly higher serum levels

of NT-proBNP and a percentage of PMNs compared to IVIG responders.[26]

CONCLUSION

IVIG resistance is common phenomenon while treating Kawasaki disease. Among the patients with acute Kawasaki disease treated with intravenous immunoglobulin (IVIG), 10-20% demonstrate resistance or incomplete effects. IVIG resistance patients have high changes of having coronary complication due to vasculitis. Being IVIG gold standard for treating Kawasaki disease, its resistance will significantly increase the complication. There are few other treatment options if in case of IVIG resistance but with increasing day chances of complication increases. With predicting IVIG resistance calculator we can predict the high risk group and we can take care accordingly. Currently 3 major scoring calculator are in use. These are very simple calculator based on laboratory findings. These scoring calculator are more sensitive and specific to Japanese population.

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