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Intravenous Immunoglobulin Resistant Kawasaki Disease

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ABSTRACT

Kawasaki disease is a systemic vasculitis that mainly affects younger children. Although the definite cause still remains unknown but the clinical and epidemiologic findings discuss an infectious cause. The prevalence of incomplete Kawasaki disease reported 15 to 36.2%, and it is more frequent in the extremes of the age spectrum. Non delayed treatment of disease should be initiated because of critical cardiac vascular complications. Up to 15% - 25% of patients with Kawasaki disease who remain febrile after administration of first dose of intravenous immunoglobin plus aspirin are classified as refractory disease. These intravenous immunoglobin resistant cases are at increasing risk for coronary artery complications. The strategy on prediction of potentially non responder and treatment of intravenous immunoglobin resistant patients is now controversial but some useful points were recommended.

Introduction

Kawasaki disease (KD) is a systemic vasculitis that mainly affects children younger than five years old .[1] Although the clinical and epidemiologic findings discuss an infectious cause, the definite cause still remains unknown. Some studies found genetic and familial tendency to KD.[2-4]However, the exact genetic factors are not yet detected and no obvious genetic risk factor is found for coronary artery lesion(CAL) in KD .[5]

Up to 75% - 85% of patients with KD become afebrile after administration of single dose of intravenous immunoglobin (IVIG) plus aspirin. Some believe that IVIG-resistant or refractory KD require additional treatments to prevent increasing risk for coronary artery lesion (CAL) .[6-8] Increased diagnosis of KD revealed high incidence of refractory KD .[9-11]

KD still remains the major cause of acquired children heart disease in developed countries .[12] CAL is the most serious complication of KD that includes coronary artery aneurysm, myocardial infarction, coronary artery fistula and coronary artery dilatation .[13] Theoretically identifying potentially refractory KD or high risk patients at the time of diagnosis might lead to treat high risk KD with combination of adjunctive therapy such as Corticosteroid or TNF α antagonist added to IVIG in initial treatment.

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Diagnosis

According to the American Heart Association (AHA), the clinical manifestation of typical KD are fever for more than five days and at least four of the following: bilateral bulbar conjunctival injection without exudates, mucocutaneous changes of oropharynx and lips, polymorphous rashes, changes in peripheral extremities and cervical lymph node enlargement(greater than 1.5cm) and exclusion of other similar diseases .[14,15]Another diagnostic guideline for KD published by Japanese KD research committee that has 6 optional principal signs includes fever for more than five days, bilateral bulbar conjunctival injection, changes in lips and oral cavity, polymorphous exanthema, changes in peripheral extremities and enlargement of cervical lymph node (without defined size) .[16]

Atypical and Incomplete KD

It seems complete and incomplete KD are situated on two sides of a continuous spectrum .[17]

"Atypical KD" and "incomplete KD" has been used for nomination of cases with incomplete presentation of the disease. But recently proposed that the term "Atypical KD" should be used for those who present unusual complication of KD, such as: lung infiltration or renal failure .[18-21]

Within the KD cases, incomplete KD prevalence reported 15 to 36.2% [18,19,21-26] and it is more frequent in the extremes of the age spectrum (≤1 years old, or ≥5 to 9 years old) .[19,21]

Because of more complications in delayed diagnosed KD, especially in coronary artery, the AHA and Japanese Ministry of Health published a criteria for incomplete KD in children ≥ 6 month of age. Both of these criteria suggest CAL in echocardiogram as a principal point. In the criteria established by AHA, fever must continue for at least 5 days and 2 or 3 of five optional signs must be presented [27] and in the Japanese criteria four of six principal criteria must be presented .[16]

An additional diagnostic algorithm recommended by the AHA for incomplete KD consists of six laboratory and three supporting echocardiographic points (Table 1).

Treatment

Non delayed treatment of KD should be initiated because of critical cardiac vascular complications, even if the diagnosis is not exactly definite.[27]

The most recommended initial therapy is Aspirin and IVIG during the first 10 days of signs .[13,27] CAL frequently will happen if therapy is delayed, however, therapy should start at any time if the first 10 days are missed.[27]

Aspirin: The first medication is aspirin and should be used in anti-inflammatory high dose (80-100 mg/kg/day)[6]or-more often in Japan and Eastern Asia- anti-inflammatory low dose (30-50 mg/kg/day)[28] within febrile phase and usually reduces to anti platelet dose (3-5mg/kg/day) after the acute febrile phase and continue until laboratory results return to normal range, unless CAL is detected, although some studies reported that aspirin in acute phase of KD could not improve the IVIG response, fever period or CAL incidence .[29]Chemical hepatitis, transient hearing loss, Reye syndrome are the most common side effect of Aspirin. It is noted that Ibuprofen could antagonize the anti-platelet function of low dose Aspirin .[27,30]

IVIG: Other necessary medication in acute phase of KD is high dose of IVIG (2g/Kg/single dose) that is shown to be useful for decreasing the CAL .[27]Although treating with aspirin plus IVIG could reduce the risk of CAL in approximately 85-95% of cases. Some studies report 15-25% of continued fever after this medications and a possibility of CAL. From the first administration of IVIG its dosage was changed and it was revealed that IVIG helps inreducing the symptoms, but CAL increased by elevation of IVIG dose up to 2g/kg .[31,32]

The most prevalent side effect of IVIG are rash, fever, nausea, hypotension, high solute load, over volume of intravascular fluid, hemolysis, headache and potential risk for transmission of blood borne pathogen.

Steroids: Glucocorticoids newly revised in adjunctive treatment of KD [16] especially in the cases expected to resist IVIG plus aspirin therapy in conditions of relapsed or refractory KD .[33,34] Although a report by Kato et al [65] showed that steroids might worsen CAL, later trials noted benefit

Table 1. additional laboratory and echocardiographic points for diagnosis of incomplete KD [27]

Additional laboratory points(more than 3 positive points support the diagnosis of KD)
1. Serum Albumin ≤3 g/dl
2. Anemia for age
3. Elevation of Alanine aminotransferase
4. Platelets after 7 days≥450000 /mm3
5. WBC ≥15000 /mm3
6. Urine WBC ≥10 /HPF
Additional echocardiographic points (any of these 3 points support the diagnosis of KD)
1- Z score of LAD or RCA ≥2.5
2- Coronary artery aneurism (by Japanese Ministry of Health Criteria)
- internal lumen diameter:
>3 mm in children < 5 yr.
>4 mm in children > 5 yr.
- of a segment measures ≥1.5 times that of an adjacent segment
- Clearly irregular coronary lumen
3- Three of the following:
- perivascular brightness of coronary artery(CA)
- lack of tapering of CA
- decreased LV function
- mitral regurgitation
- pericardial effusion
- Z score in LAD or RCA of 2 to 2.5

LCA: Left coronary artery
RCA: Right coronary artery
CA: coronary artery
LV: Left ventricle
HPF: High power field
Yr: years old

of cortons administered in primary treatment of KD .[33,36,37]

Dose and prescription of Glucocorticoids vary in different trials recently intravenous pulse methylprednisolone 30mg/kg for one to three days is used with or without consequence oral prednisolone. Another regimen is oral prednisolone 2-3 mg/kg for two weeks followed by 1.5 mg/kg for the next 2 weeks .[33,37]

Common early onset complication of Glucocorticoids is hypertension, bradycardia, hypothermia, thrombosis, femoral head necrosis, convulsion, secondary infection, gastrointestinal bleeding, hyperglycemia, hyponatremia and hyperkalemia.

Because of markedly increase of TNFα in KD, especially in patients who develop CAL, researchers try to show whether the TNF-α inhibitors such as infliximab reduce the complications of KD or eliminate its activity. Some studies mentioned some benefits like elimination of fever and C reactive protein (CRP) level but it did not have the same effect on CAL .[38,40] The major side effects of infliximab are anaphylaxis and immunosuppression and the minor side effects are included headache, nausea and upper respiratory tract infections.

Miura et al and Eberhard et al found that infiltration of CD8+ T cells around the affected artery was increased in CAL followed by KD .[41]For this reason they used calineurin inhibitors such as Cyclosporine A and Tacrolimus used for adjunctive therapy of KD .[8,42]

Major unwanted effects of cyclosporine A include hepatotoxicity, nephrotoxicity, hypertension, seizure, and electrolyte imbalance.

Plasmapheresis and plasma exchange are other medical treatments that shown could lead to dramatic response but technical difficulties and hazards limits using this therapeutic only for patients resisting other available regimen.[43]

Other medical interventions such as pentoxyfylline, Ulinastatin, Abciximab, Cyclophosphamide[44],Methotrexate[45] and Etanerceptare used to treat KD. Limited studies exist regarding using these agents, but these medications could be considered in treating unresponsive KD. Harada et al used Heparin (15-20 units/kg/hour) in combination with intravenous methylprednisolone (IVMP) to prevent thromboembolic events .[46] Dipyridamole and clopidogrel as antiplatelet, warfarin and low-molecular-weight heparin as anticoagulant and statins are also used as protection against ongoing atherosclerosis.[47]

Resistance and Relapse

Patients with refractory KD remain febrile within 48 hours of receiving 1 dose of IVIG or have recrudescence of fever after 48 hours of IVIG therapy.[6]

Different centers reported resistance to initial treatment with IVIG from 9.4% up to 38%. Recent studies indicated a relationship between some laboratory and demographic characteristics for identifying refractory KD, such as: age, sex, pretreatment illness duration, initial abnormal echocardiographic results, levels of ESR, CRP, sodium, lactate dehydrogenase, albumin, alanine aminotransferase, percentage of hemoglobin, eosinophil, neutrophil, lymphocyte, band cell, platelet count, and T-Cell activity (Table 2).[48-52]

Delayed treatment or resistance to initial therapy more frequently lead to CAL. Usually the Japanese ministry of health criteria or American heart association criteria is used for defining CAL .[27]

Kobayashi et al [9] reviewed thirteen variables in KD patients including: duration of illness at initial treatment, gender, age in months, neutrophils percentage in white blood cells, platelet count, aspartate (AST) and alanine (ALT) aminotransferase, total bilirubin, sodium, chloride, total protein, albumin and C-reactive protein(CRP).This multicenter study reviewed546 cases of KD, retrospectively to develop their predictive model and 204 cases prospectively to test the accuracy of prediction. Initial treatment included IVIG (1g/kg for two consecutive days), aspirin (30mg/kg/day) and dipyridamole (2mg/kg/day). IVIG non responder is defined as someone who has fever after 24 hours from initial therapy or has recrudescence of fever after an afebrile period. Sensitivity and specificity of initial created scoring model in accuracy tester group was 90% and 77%, respectively. Then they constructed further simplified scoring model using both groups' data and suggested:2 points for sodium≤133, 2 points fordays of illness at initial tratment≤4, 2 points for AST≥100 IU/L, 2 points for neutrophils %≥80%, 1 point for CRP≥10 mg/dl, 1 point for age≤12 months, 1 point for platelet count≤ 300000/mm^3.According to these scoring, low risk strata was sum of points 0 to 3, high risk strata was between 3 to 7,and the score ≥7 was considered very high risk. The occurrence of IVIG nonresponder was 75%, 43% and 5% in the very high risk, high risk and low risk group, respectively and the occurrence of CAL was 36%, 16% and 1% in the very high risk, high risk and low risk group, respectively.

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Sleeper et al [48] carried out a randomized double blind, placebo-controlled trial of added intravenousmethyl prednisolone (IVMP; 30mg/kg in 2-3 hours) to the standard primary treatment of KD (IVIG; 2g/kg and aspirin; 80-100mg/kg) in North America.They compared the Kobayashi, Egami and Sano published risk score for prediction of response to IVIG treatment in a population in North America.

The Kobayashi score provide a significant predictor of coronary artery (CA) size changes at 1 and 5 weeks in the subjects not receiving primary steroid therapy. But Egami and Sano scores were not associated with CA size.

Primary steroid therapy in the group who were retreated only with IVIG reduced CA abnormality compared with those who did not receive steroid in primary KD treatment. However, there is not enough evidence regarding the benefits of adjuvant therapy in high or low risk cases. However, there is not enough evidence regarding the benefits of adjuvant therapy in high or low risk cases. However, there is not enough evidence regarding the benefits

Table 2. Scoring suggested by studies for prediction of High risk or Non-responder KD

Author(s)	Year/ Location	Detail/ Number of cases	Point		Value	Suggested Scoring	Sensitivity%	Specificity%	Neg. Pred. Val%	Pos. Pred. Val%
Kobayashi et al[9]	2000 to 2006 Korea	Retrospective (546 cases) and prospective (204 cases)	sodium≤133 days of illness at initial tratment≤4 AST≥100 IU/L neutrophils%≥80% CRP≥10 mg/dl age≤12 months platelet count≤ 300000/mm3		2 points 2 points 2 points 2 points 1 points 1 points 1 points	very high risk : score ≥7 high risk: 6≥ score ≥4 low risk: score ≤3	86	67		
Egami et al [49]	1998 to 2004 Japan	Retrospective (320 cases)	ALT≥80 IU/L age≤12 months days of illness at initial tratment≤4 platelet count≤ 300000/mm3 CRP≥8 mg/dl		2 points 1 points 1 points 1 points 1 points	high risk: score ≥4 low risk: score ≤3	78	76	96	32
Sano et al [55]	1999 to 2000 Japan	Retrospective (112 cases)	CRP≥7 mg/dl Total Bilirubin≥0.9 AST≥200 IU/L		1 points 1 points 1 points	High risk: 2 Points or more	77	86	94	59
Nakano et al [56]	1977 to 1985 Japan	Retrospective (78 cases)	Age	<1 yr 1-2 yr >2 yr	-1 0 +1	High risk: Total Score is Negative Low risk: Total Score is Zero or Positive				
			CRP (qualitative)	0-1 plus 2-4 plus 5 plus 6 plus	+2 +1 0 -3					
			Platelet count	<300000 >300000	-1 +1					

Neg. Pred. Val: negative predict value
Pos. Pred. Val: positive predict value

of adjuvant therapy in high or low risk cases. However, there is not enough evidence regarding the benefits of adjuvant therapy in high or low risk cases. They found no difference between steroid therapy effects on CAL prevalence in the high and low risk subgroup.

The sensitivity of these three scores for detecting IVIG resistance was low (33%, 42%, 42% for kubayasi, Egami and Sano, respectively) and the specificity was moderate to high (85% , 87%, 87% for kubayasi , Egami and Sano, respectively).This study suggested that using these scoring criteria will show most KD patients who are at low risk, but most patients do not need more observation or additional therapies to reduce the heart complications. The correlation between CA outcomes and the risk level was low. Also, the serum albumin level and male gender are two independent risk factors not included in these three risk scoring systems.

Do et al [53] retrospectively evaluated 77 patients with typical KD and reported that other Korean criteria suggested by Kobayashi et al could help in predicting non-responders KD, they also showed that high percentage of neutrophils and low percentage of lymphocytes during the subacute phase of the disease could predict IVIG resistance. Ashouri et al found that presence of serum albumin≤3 mg/dl, band cell >10% and existence of CAL at diagnosis are significantly more frequent in non-responder cases .[54]

Treatment of refractory KD

A secondary dose of IVIG (1 to 2 g/Kg) is frequently used for treatment of refractory KD .[27] But more prolonged period of fever as a symbol of remaining inflammation after this therapy. Several studies showed at least no increase in CAL and more decrease in fever period after treatment with IVIG plus IVMP 30mg/kg for 1 to 3 days .[57]Four randomized studies that used IVIG plus corticosteroid therapy and aspirin, suggest that this treatment decreased the need for re-treatment with IVIG and did not increase the risk of CAL.[6]

A multicenter randomized, open-label, blinded-end point's trial in Japan added oral corticosteroid (prednisolone 2mg/kg) to IVIG (2g/kg) and aspirin(30mg/kg). It compared the baseline characteristic of 121 cases and found significant decrease in CAL and a more rapid suppression of fever and inflammatory markers. It suggested that adjuvant corticosteroid therapy could reduce the risk of CAL in potentially high risk cases .[58]

Ogata et al [59] compared additional IVIG(2g/kg) and pulse methyl prednisolone (IVMP, 30mg/kg/day for 3days) therapy in 27 cases of refractory KD in Japan. All patients were treated initially with IVIG (2g/kg) plus aspirin (30 mg/kg/day).They observed a significant improve in fever relief and count of CAL was found to be lower in IVMP group, however, no significant difference was seen in CAL between the groups.

Hashino et al [57] used a second dose of IVIG (1g/kg) in 35 unresponsive cases (after IVIG 2g/kg plus aspirin (30mg/kg/day). Seventeen patients (6.5%) who did not respond to retried IVIG therapy were divided into two groups to receive the third dose of IVIG (1g/kg) or steroid pulse therapy (methylprednisolone 20mg/kg). This trial found significant shorter period of fever and lower medical costs in steroid group but there was no significant difference in CAL between the groups although transient coronary artery dilatation was detected in the course of therapy.

Miura et al [46] prospectively evaluated patients who were unresponsive to two subsequent dose of IVIG (2g/kg/dose). These cases received IVMP (30mg/kg/day) for three days, followed by one week of oral prednisolone (1-2 mg/kg/day). This strategy decreased the risk of CAL in refractory KD thereby.

Cyclosporine A and tacrolimus as a calineurin inhibitor were used by Adriana et al [60] and Suzuki et al [42] in a demographic and clinical matched data trial. They reported this treatment as a safe and effective therapy for refractory KD.

An alternative therapy in refractory KD is infliximab 5mg/kg [40, 61, 62] which is reported to be useful in immunologic disorders that are mediated by TN-Fα.

Conclusion

The criteria for typical disease is well approved, however, more investigations are needed for determining such criteria for incomplete and atypical KD. After the years the aetiology of KD still remains unknown, therefore the best treatment of KD especially in refractory cases and identifying potentially nonresponder individuals at the time of diagnosis is await for further researches on different races, demographic factors and maybe geographical

regions. In reviewed articles some simple laboratory or demographic points were offered for predicting refractory cases to classic IVIG regimen or high risk patients for development of CAL, such as high serum ALT, low platelet count, low serum sodium, high CRP, low age, high neutrophil percentage and if days of illness at initial treatment are four or less. The aforementioned points are of great benefit, but effective prevention of CAL depends on worldwide and further trials to establish more reliable predictors and more effective treatments.

Currently, aspirin and IVIG are the most recommended therapies for initial treatment of KD. Renunciation of steroids is somewhat troublesome due to having dramatic effect on treatment of other immunologic diseases even in primary treatment of KD. However, more studies should be carried out to prove its safety and finding the best therapeutic dosage. The other mentioned therapeutics reserved for unusual situation such as refractory disease need further investigations regarding their efficacy for the treatment of Kawasaki disease and reducing its complications.

Conflict of Interest

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