Usefulness of initial single intravenous immunoglobulin therapy for Kawasaki disease

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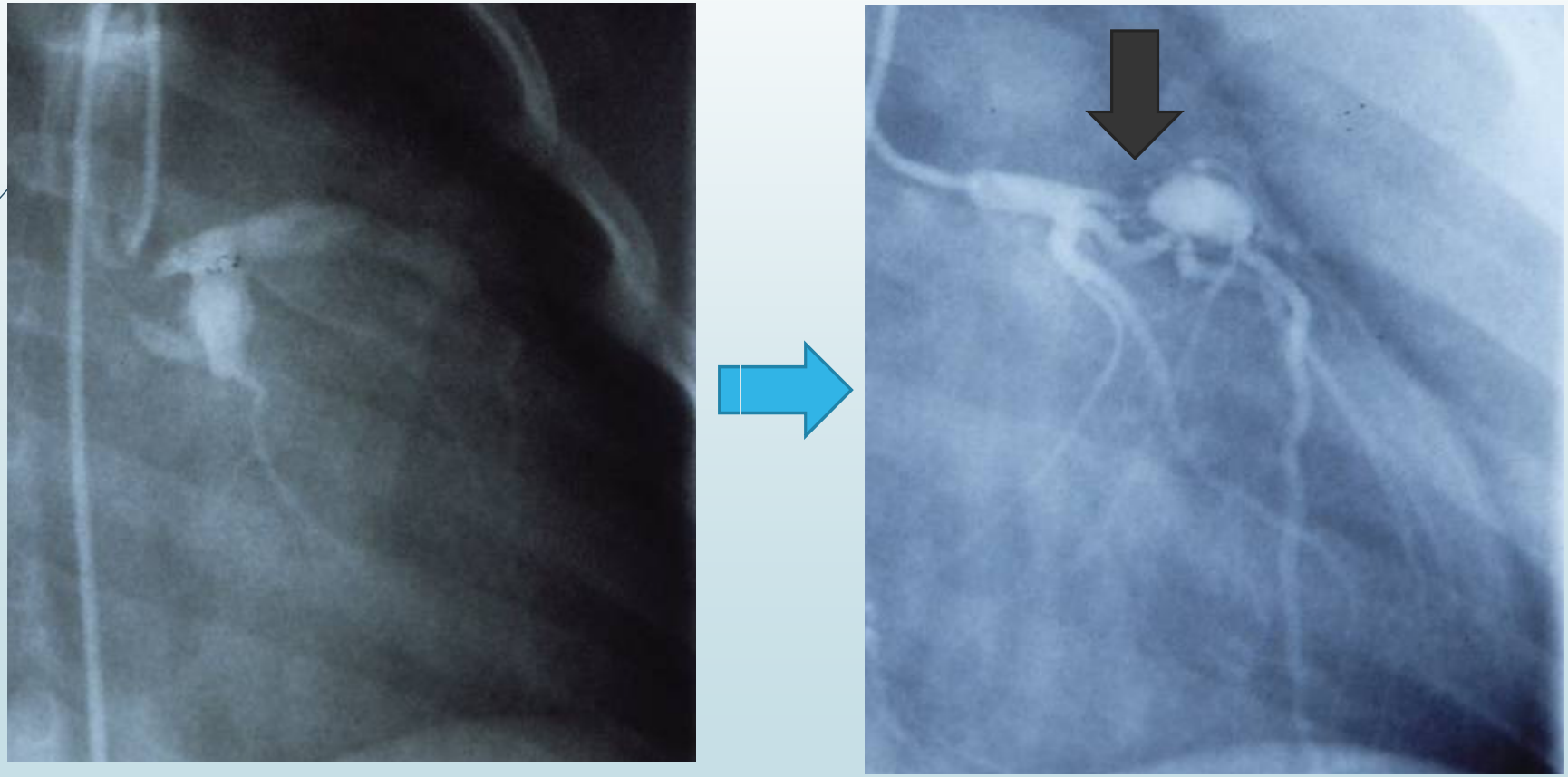
Kawasaki disease

- Kawasaki disease is an acute systemic vasculitis of unknown cause that affects mainly infants and children.
- Coronary artery lesions (CAL) are one of the most important complications of this disease.

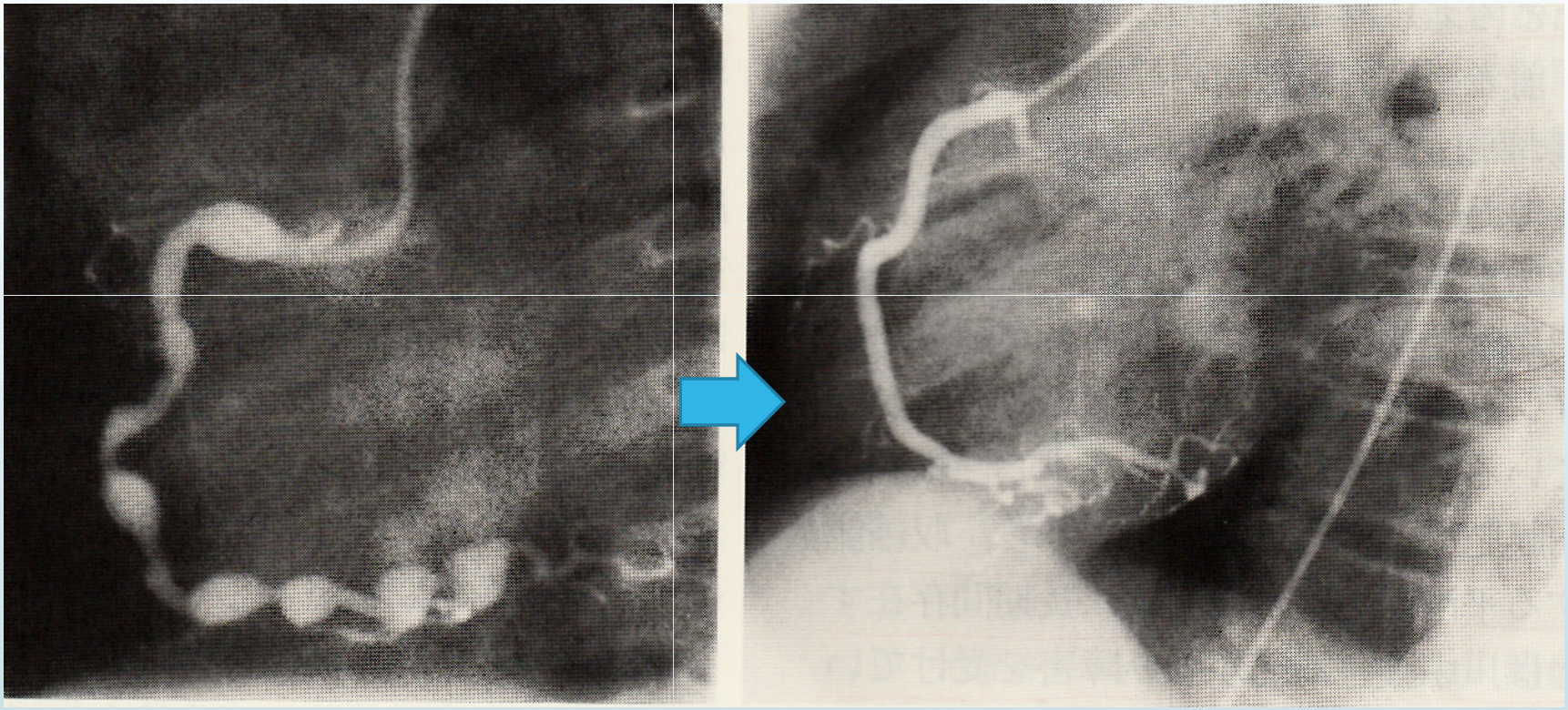
Clinical features of coronary artery lesions (CAL) caused by Kawasaki disease

- During acute phase (before day 30 from disease onset) --- coronary artery aneurysms develop.
- During convalescent phase (after day 30
- Large aneurysms develop into subsequent stenosis.
- Small aneurysms regress without leaving stenotic lesions.

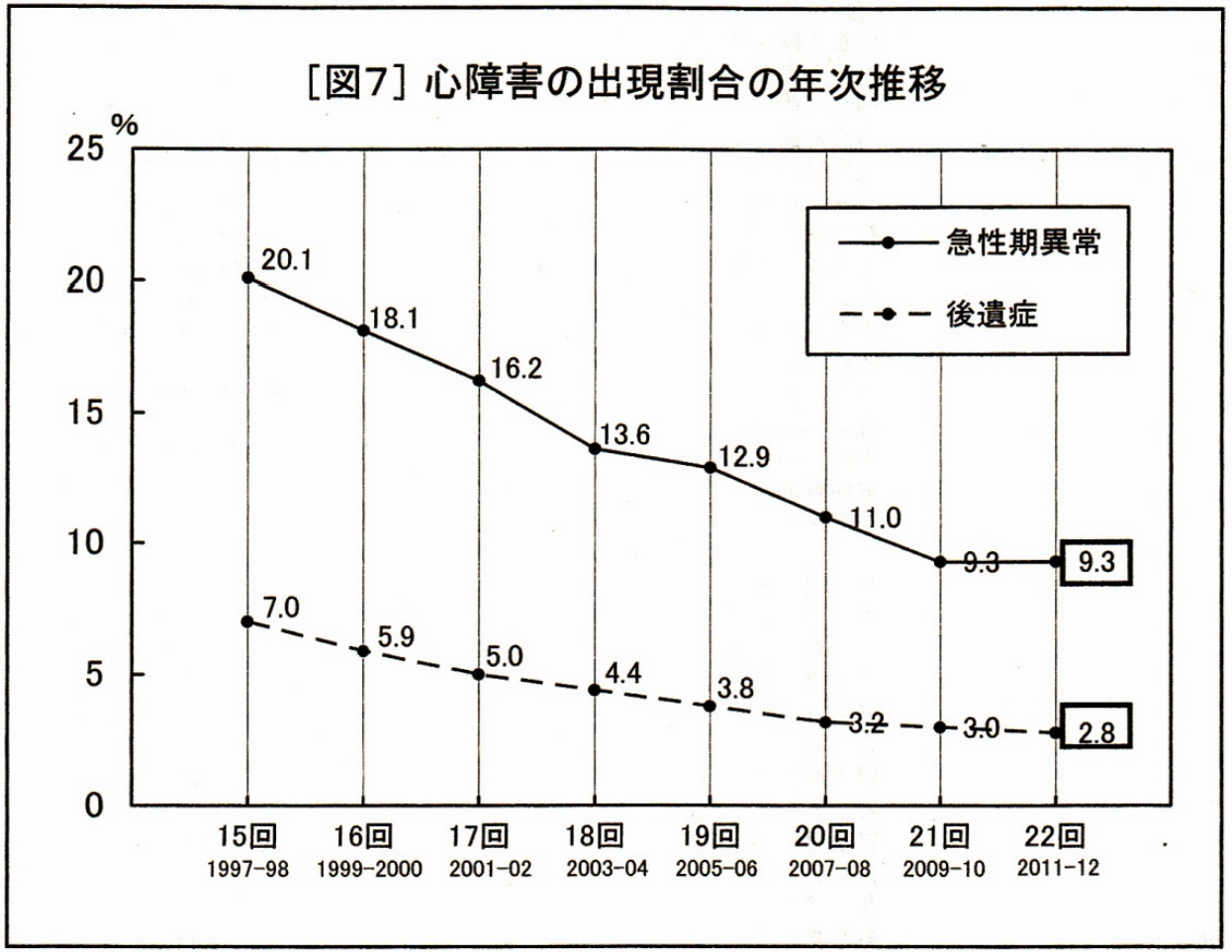
Large CAL developed into subsequent stenosis



Small CAL regressed without stenotic lesions



Japanese nationwide survey for Kawasaki disease: decreasing prevalence of CAL



Immunoglobulin therapy for Kawasaki disease

- Treatment with intravenous immunoglobulin (IVIG) therapy reduces the occurrence of CAL caused by Kawasaki disease.
- However, the appropriate therapy for the prevention of large CAL has not been established.

3 studies

- Effects of anti-inflammatory drugs on intravenous immunoglobulin therapy in the acute phase of Kawasaki disease.
- Prevention of large coronary artery lesion caused by Kawasaki disease.
- Background factors associated with the complications of coronary artery lesions caused by Kawasaki disease.

Effects of Anti-Inflammatory Drugs on Intravenous Immunoglobulin Therapy in the Acute Phase of Kawasaki Disease.

Toshimasa Nakada
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Introduction-1

- Standard therapy for Kawasaki disease is the combination of intravenous immunoglobulin (IVIG) and aspirin.
- Platelets are activated during the acute phase of Kawasaki disease which provides biological plausibility for antiplatelet therapy [Circ J 2014].

Introduction-2

- However, the role and impact of anti-inflammatory drugs (ADs) including high- or medium- dose aspirin on IVIG therapy during the acute phase of Kawasaki disease remain unclear.
- Two studies have shown that ADs may be unnecessary in the acute phase of Kawasaki disease [Pediatric 2004, Korean Circ J 2013].

Introduction-3

- The hypothesis of this study was that
- ADs are unnecessary in the acute phase of Kawasaki disease and negatively impact the effects of IVIG on CAL suppression.
- This study aimed to investigate the necessity of ADs and their impact on initial IVIG therapy.

Methods-1

- This retrospective study included 182 consecutive patients (94 boys 88 girls; mean age 2 years and 9 months; range 2 months to 13 years 3 months)
- who received IVIG therapy for Kawasaki disease between January 1999 and September 2013 at the Department of Pediatrics, Aomori Prefectural Central Hospital.

Methods-2

- All patients were divided into S and T groups.
- ***The S group*** comprised 111 patients who received initial IVIG therapy with **delayed** administration of ADs,
- while **the T group** comprised 71 patients who received **concomitant** ADs with IVIG.

Methods-3

- In the S group, ADs were initiated within 24 h after the end of initial IVIG infusion.
- The regimen of the S group was used after 2004.
- Some patients received the therapy by the regimen of the S group between 2004 and 2008.
- After 2009, this regimen was used to all patients.

ADs Therapy

- The choice between aspirin (A) and flurbiprofen (F) was made by each doctor after consideration of the patient's liver function and the risk of Reye syndrome at the influenza pandemic.
- Flurbiprofen was more commonly used before 2009.

A dose of aspirin and flurbiprofen

- Aspirin was initiated at a dose of 30 mg/kg/day and decreased to 5–10 mg/kg/day when patients became afebrile.
- Flurbiprofen was initiated at a dose of 3 – 5 mg/kg/day and decreased to 3 mg/kg/day when the patient became afebrile.

IVIG Therapy

- An initial 2g/kg/day IVIG regimen on the fifth day of illness was used as the first-line therapy when possible.
- The indication for additional therapy in resistant patients was determined between 48 and 72 h after the end o the initial IVIG infusion.

Additional Therapy

- Indication diagnosis for additional therapy was made according to clinical parameters, including body temperature, general condition, and laboratory data.
- The second-line therapy was additional IVIG therapy and the third-line therapy was urinastatin infusion.

Definition of responsiveness and resistance to IVIG Therapy

- Patients who responded to IVIG therapy were defined as those who became afebrile (temperature < 37.5℃ for 24 h) within 24 h after completion of initial IVIG infusion.
- IVIG-resistant patients were defined as those not meeting this criteria.

Diagnosis of CAL

- CAL was diagnosed by echocardiography according to the Japan Ministry of Health and Welfare criteria .
- CAL was defined as an artery diameter exceeded 3 mm in a child aged below 5 years or exceeded 4 mm in a child aged years or older. Transient CAL was defined as the disappearance of CAL within 30 days of illness.

Results about therapy

- Steroids were not administered to any patients.
- The initial IVIG regimens of 2 g/kg/day and 1 g/kg/ day were used in 176 patient and 6 patients, respectively.
- Initial IVIG therapy resistance occurred in 45 of 182 patients (25%), and
- 13 patients (7 %) received additional IVIG
- Three patients received urinastatin.

Results about CAL

- The prevalence of CAL up to day 30 of illness was 7% (12 / 182); after 30 days, it was 2 % (4 / 182).
- The maximal internal CAL diameters were within 4mm in all patients.

The comparison of clinical findings between the S and T groups; *median (minimum – maximum)

	S group (n = 111)	T group (n = 71)	P - value
Sex (male/ female)	52 /59	42 /29	>0.05
Age of onset (month)	24 (2 – 159)*	22 (3 – 114)*	>0.05
Year of onset			
1999 – 2003	0 (0%)	42 (59%)	<0.001
2004 – 2008	33 (30%)	29 (41%)	>0.05
2009 – 2013	78 (70%)	0 (0%)	<0.001
Egami score	1 (0 – 4)* (n=110)	1 (0 – 5)* (n=70)	>0.05

The comparison of clinical findings between the S and T groups

	S group (n = 111)	T group (n = 71)	P - value
Incomplete type	11 (10%)	5 (7%)	>0.05
Leukocyte count (/mm^3)	12,700 (3,900 – 30,900)*	13,750 (4,200 – 27,700)*	>0.05
CRP(mg/dL)	6.81 (0.16 –26.32)*	7.29 (1.19 –26.47)*	>0.05
Alb(g/dL)	3.50 (2.70 – 4.40)*	3.70 (2.50 – 4.30)*	<0.001
Na(mEq/L)	135 (123 – 141)*	136 (128 – 143)*	>0.05
AST(IU/L)	35 (15 – 648)*	30 (13 – 302)*	>0.05
ALT(IU/L)	29 (8 – 485)*	24 (6 – 498)*	>0.05

The comparison of clinical findings between the S and T groups

	S group (n = 111)	T group (n = 71)	P - value
IVIG			
Start day of illness	5 (4 – 16)*	5 (3 – 10)*	>0.05
Protocol			
1 g/kg	1 (0%)	5 (7%)	0.034
2 g/kg	110 (100%)	66 (93%)	0.034
Resistance	26 (23%)	19 (27%)	>0.05
Additional IVIG	7 (6%)	6 (8%)	>0.05
Aspirin/Flurbiprofen (A/F)	62/49	17/54	<0.001
Urinastatin	0(0%)	3(4%)	>0.05

The comparison of clinical findings between the S and T groups

	S group (n = 111)	T group (n = 71)	P - value
CAL	1(1%)	11(15%)	<0.001
Transient dilation	1(1%)	7(10%)	0.022
CAL after 30 days of illness	0(0%)	4(6%)	0.022

Logistic regression analysis for CAL

variables	P - value	Odds ratio	95% CI
the S group	0.009	0.061	0.008 – 0.491
2g/kg/day IVIG	0.015	0.099	0.015 – 0.641
the S group	0.025	0.087	0.010 – 0.732
2g/kg/day IVIG	0.030	0.120	0.018 – 0.812
A/F	0.216	0.257	0.030 – 2.215
Onset after 2009	0.164	0.220	0.026 – 1.854
2g/kg/day IVIG	0.011	0.094	0.015 – 0.584
A/F	0.102	0.169	0.020 – 1.426

Discussion-1

- This study identified a possible negative impact of ADs on initial IVI therapy in the acute phase of Kawasaki disease.

Discussion-2

- It was previously reported that ADs, including aspirin, affected the immunological function of T-cells .
- A recent study suggested that the pathway including T cells ma play a role in the mechanism of action of IVIG .

Discussion-3

- Furthermore, a recent immunologica study highlighted that T cell activation in the early and middle stages was involved in the mechanism underlying cardiovascular injury in Kawasaki disease .
- These findings suggest that ADs can alter the effects of IVIG on Kawasaki disease.

Conclusions

- Aspirin and flurbiprofen appeared to hav a negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease.
- Initial single IVIG therapy with delayed administration of ADs may be useful for the suppression of CAL due to Kawasaki disease.

Prevention of large coronary artery lesions caused by Kawasaki disease

Toshimasa Nakada

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Introduction-1

- Myocardial ischemia due to CAL is one of the most important complications caused by Kawasaki disease.
- Long-term follow-up studies have shown that a maximum CAL size >5 mm was a statistically significant predictive risk factor for myocardial ischemia (Clin Res Cardiol 2009).
- Therefore, the prevention of CAL of >5 mm ma be an important goal in the acute treatment of Kawasaki disease.

Introduction-2

- Combination regimens of IVIG and other drugs including steroids and infliximab have been tried as the initial therapy (Lancet 2012, 2014).
- However, the treatment for the prevention of large CAL has not been established.

Introduction-3

- On the other hand, there have not been enough studies about initial single IVIG therapy in spite of the safety and effectiveness of this therapy.
- Initial single IVIG therapy with delayed administration of ADs may be beneficial in the suppression of CAL caused by Kawasaki disease .

Introduction-4

- The hypothesis of this study was that initia single IVIG therapy with delayed administration of ADs may be useful in the prevention of large CAL that were larger than 5 mm.
- Accordingly, this study investigated the outcome of CAL in patients that received this approach for Kawasaki disease.

Methods-1

- This retrospective study included 132 consecutive patients (64 boys, 68 girls; the mean age was 2 years and 10 months, and the age range was 2 months to 13 years and 3 months)
- who received 2g/kg/day initial IVIG therapy with delayed administration of ADs for Kawasaki disease between January 2004 and December 2014 at the Department of Pediatrics, Aomori Prefectural Central Hospital.

Additional Therapy

- The second-line therapy was additional IVIG therapy and the third-line therapy was urinastatin infusion.
- Plasma exchange had been adopted in 2014 as another third-line therapy option.

Definition of Relapse of Kawasaki disease

- After a patient became afebrile during the acute phase,
- an exacerbation or reappearance of major symptoms without other pyrogenic disease was defined as a relapse.

Results about therapy-1

- 74 patients received aspirin and 58 patients received flurbiprofen after completion of initial IVIG infusion.

Results about therapy-2

- Initial IVIG therapy resistance occurred in 31 of 132 patients (23%), and 10 patients (8%) received additional IVIG; nine patients for initial IVIG resistance and one patient for relapse, respectively.
- One patient received urinastatin and one patient received plasma exchange as third-line therapy.

Results about CAL

- Before day 30, the prevalence of CAL was 2% (2/132); after day 30, it was 1% (1/132).
- The maximal internal CAL diameters were 4.8 mm (Z score = 6.3) among all patients.

The patient with the largest CAL diameter (Patient 1)

- had CAL on day 8, and she received a plasma exchange on day 9 at the hospital of Hirosaki University School of Medicine for 3 days.
- Her CAL diameter was 4.8 mm on day 21.
- However, echocardiography on day 52 showed the regression of CAL and normal internal coronary artery size.
- The selective coronary arteriogram performed at 7 months after disease onset revealed no abnormal findings.

Table 1. Comparison of results regarding prevention of large coronary artery lesions among four studies

	Present study	Previous studies		
		Study 1	Study 2	Study 3
IVIG protocol	2 g/kg	2 g/kg	2 g/kg	2 g/kg
ADs	Asp or Flur	Asp	Asp, Asp + Pred	Asp, Asp + Inf
	(n = 132)	(n = 273)	(n = 121) (n = 121)	(n = 98) (n = 98)
Use of ADs	delayed	concomitant	concomitant	concomitant
Prevention of large CAL	Yes	No	No No	No No

Study 1: *N Engl J Med* 1991; 324: 1633–9, Study 2: *The Lancet* 2012; 379: 1613–20, Study 3: *The Lancet* 2014; 383: 1731–38,

IVIG: intravenous immunoglobulin, ADs: anti-inflammatory drugs, Asp: aspirin, Pred: prednisolone, Inf: infliximab, Use of ADs: use of ADs to initial IVIG therapy, Large CAL: large coronary artery lesions with internal diameters of larger than 5 mm or of larger than Z score 6.5

Discussion

- This study identified the usefulness of initial single IVIG therapy with delayed administration of ADs for the prevention of CAL of more than 5 mm in size and the prevention of subsequent coronary artery stenosis caused by Kawasaki disease.

Discussion

- As shown in Table 1, use of delayed administration of ADs appeared to be the important factor for prevention of large CAL.
- The different type of ADs did not appear to be the important factor.

Logistic regression analysis for CAL

variables	P - value	Odds ratio	95% CI
the S group	0.009	0.061	0.008 – 0.491
2g/kg/day IVIG	0.015	0.099	0.015 – 0.641
the S group	0.025	0.087	0.010 – 0.732
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2g/kg/day IVIG	0.011	0.094	0.015 – 0.584
A/F	0.102	0.169	0.020 – 1.426

Discussion

- ADs appeared to have a negative impact on the suppressive effects of initial IVIG therapy on CAL development in the acute phase of Kawasaki disease (Pediatr Cardiol 2015).
- Therefore, knowledge regarding the technique of using ADs may be a breakthrough for the prevention of large CA caused by Kawasaki disease.

Discussion

- Patients who received initial single IVIG therapy with delayed administration of ADs may not receive a negative impact on the suppressive effects of ADs to IVIG therapy until the start time of ADs administration.
- This may be a mechanism that the combination order of initial IVIG therapy with administration ADs may lead to the prevention of large CAL.

Conclusion

- Initial single IVIG therapy with delayed administration of ADs may be useful for the prevention of CAL that are more than 5 mm in size during the acute phase of Kawasaki disease.

Background factors associated with the complications of coronary artery lesions caused by Kawasaki disease

Toshimasa Nakada

Clinical Medicine Research
4:127-131,2015 (open access)

Methods

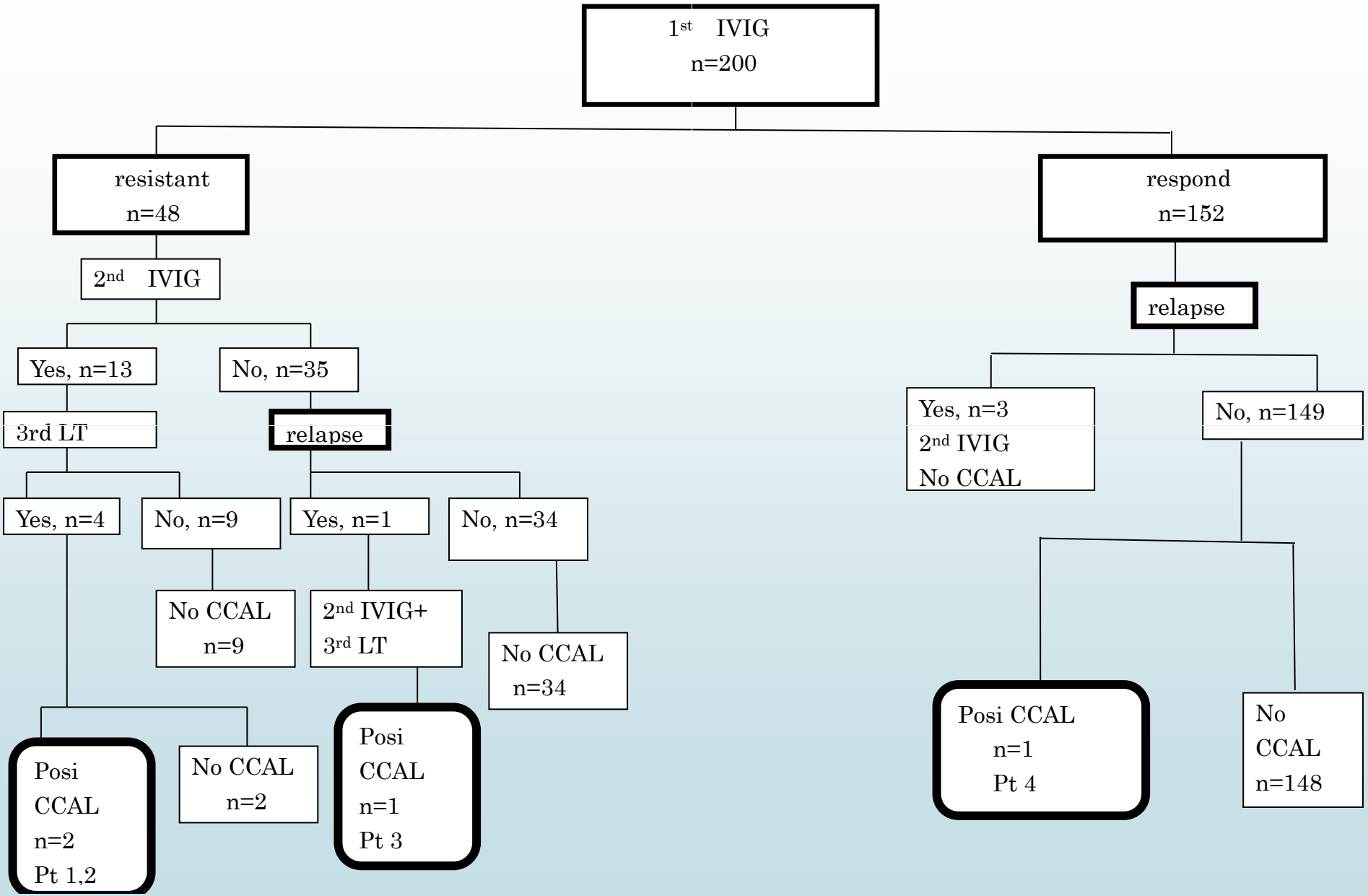
- This retrospective study included 200 consecutive patients (105 boys, 95 girls; the mean age was 2 years and 8 months, and the age range was 2 months to 13 years and 3 months) who received initial 2g/kg/day IVIG therapy for Kawasaki disease between January 1999 and February 2015 at the Department of Pediatrics, Aomori Prefectural Central Hospital.

Methods

- This study include 134 S group patients and 66 T group patients.
- In this study, an initial single IVIG therapy was the regimen used to treat the patients in both the S and T groups.

Results about CAL

- The prevalence of CAL before day 30 was 5% (10/200); after 30 days, it was 2% (4/200).
- The prevalence of CAL before and after 30 day of illness between the S vs. T groups were 2/134 vs. 8/66 (P = 0.003) and 1/134 vs. 3/66 (P = 0.106 respectively.
- The maximal internal CAL diameters were 4.8 mm (Z score = 6.3) among all patients (patient


1st IVIG
n=200
resistant
n=48
respond
n=152
2nd IVIG
relapse
Yes, n=13
No, n=35
Yes, n=3
2nd IVIG
No CCAL
No, n=149
3rd LT
relapse
Yes, n=4
No, n=9
Yes, n=1
No, n=34
No CCAL
n=9
2nd IVIG+
3rd LT
No CCAL
n=34
Posi
CCAL
n=2
Pt 1,2
No CCAL
n=2
Posi
CCAL
n=1
Pt 3
Posi CCAL
n=1
Pt 4
No
CCAL
n=148

Background factors associated with complications of CCAL

No of patients	Background factors
1	Persistent fever after resistance o initial IVIG therapy
2	Persistent fever after resistance o initial IVIG therapy
3	Relapse
4	Response for initial IVIG therapy

Discussion

- The background factors for the development of CAL complications were variable.
- An initial single IVIG therapy may be usefu in the prevention of large CAL caused by these factors in the acute phase of Kawasaki disease.

Discussion

- A single IVIG therapy does not modify the clinical course of Kawasaki disease.
- This characteristic permits clinicians to easily manage the treatment progress and to provide additional therapies at the appropriate times in the variable clinical courses.

Conclusions

- Variable factors including IVIG resistance, responsiveness and relapse were associated with CAL complication.
- Initial single IVIG therapy may be useful for the prevention of large CA caused by different factors of Kawasaki disease.

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Thank you for your attention.