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Guidelines

Revision of diagnostic guidelines for Kawasaki disease (6th revised edition)

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Purpose and background of the revision

The diagnostic guidelines for Kawasaki disease (KD) were last revised in 2002[1] (5th revision). Major points of revision included: (i) the definition of fever was defined as fever persisting 5 days or more (inclusive of cases in which the fever had subsided before the fifth day in response to therapy) and (ii) to explicitly state that incomplete KD cases can have coronary artery lesions.

After the 5th revised edition of the diagnostic guidelines for KD was published, the proportion of patients receiving early treatment increased and the incidence of coronary artery lesions decreased nationwide. On the other hand, the number of incomplete KD cases increased yearly from 10% to the current level, which is greater than 20% of all KD patients.

In recent years, a standard method for expressing the coronary artery internal diameter of Japanese children was established[2] and allowed us to define coronary artery internal dimensions in terms of standard deviations from the mean, or Z scores). Incorporation of Z scores to facilitate the diagnosis of incomplete KD was a motivating factor for this revision. In the 5th edition, the section titled "Other significant symptoms or findings" was not changed; therefore, the description from the 4th edition lasted more than 30 years and was due for an update. In 2017, we consulted with the Japan Kawasaki Disease Society Steering Committee Members regarding the necessity for a revision of the 5th revised edition, and 75% of the committee members agreed to revise. The Japan Kawasaki Disease Research Center and study group for vasculitis funded by the Ministry of Health, Labor and Welfare also agreed to the revision.

In this revision, the writing group members conducted discussions from 2018 to 2019. The original draft was presented to the 38th Annual Meeting of the Japanese Society of Kawasaki Disease in Wakayama. The draft was revised again, based on the steering committee members' suggestions, and the final draft of the 6th revision was completed. In the future it will be interesting to evaluate the impact of these revised guidelines on the diagnosis of KD in Japan.

The previous 5th edition[1] was published as an article in *Japan Today* in 2005, and was titled "Diagnostic Guidelines." The recent format of the "guidelines" has changed and requires full supporting evidence; "diagnostic guidance" or "criteria with clinical findings" may be more appropriate as the title for this revision because there is not enough evidence for the diagnosis of this disease. However, as the previous title has been familiar with most pediatricians and primary care physicians, we would prefer to use the same title with only the change of the edition number from the fifth to the sixth revised edition. Additionally, because such clinicians use these guidelines as the diagnostic criteria, it is desirable to be as concise as possible and to be presented as a few brief sheets of 1 or 2 pages.

As we also believe more detailed explanations are necessary to describe each item, including many examination

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findings, an additional "guidebook" will be written by the committee members for publication.

The major changes of the revision are described below.

Principal clinical features

Several changes were made to the six principal clinical features, which have been well understood and disseminated for almost all clinicians in Japan (Tables 1–3 and Figure 1).

1. The requirement for a specific duration of fever was deleted. In Japan, more than 90% of KD patients received high dose intravenous immunoglobulin (IVIG) in a single dose. Although most pediatricians or primary care physicians know that the classic definition of KD required a duration of fever for more than 5 days, the 24th Nationwide Surveillance reports that approximately 9%, 25%, and 35% of KD patients received the first IVIG treatment on the 3rd, 4th, and 5th days of illness, respectively, and the prevalence of coronary artery lesions (CALs) has been

Table 1 Principal clinical features

1. Fever.
2. Bilateral bulbar conjunctival injection.
3. Changes of lips and oral cavity: reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa.
4. Rash (including redness at the site of Bacille Calmette-Guèrin (BCG) inoculation).
5. Changes of peripheral extremities: (Initial stage) reddening of palms and soles, edema. (Convalescent stage) periungual desquamation.
6. Non-supparative cervical lymphadenopathy.

Table 2 Definition of complete or incomplete KD

Number of principal clinical features	Coronary artery abnormalities (+)	Coronary artery abnormalities (−)
6	Complete (a)	Complete (a)
5	Complete (a)	Complete (a)
4	Complete (b)	Incomplete (d)
3	Incomplete (c)	Incomplete (d)

To diagnose complete or incomplete KD, the exclusion of other febrile illnesses is essential.

a: A patient who fulfills the criteria with five or six signs is diagnosed as complete KD.

b: A patient who fulfills the criteria with four signs and coronary artery abnormality by echocardiography (Figure 1-h) is diagnosed with complete KD.

c: A patient who has three principal clinical features with coronary artery abnormality by echocardiography (Figure 1-h) and in whom other febrile illnesses have been excluded fulfills the criteria in "c."

d: When the patients who fulfill three or four signs in the the principle clinical features without coronary artery dilation but with some features from the list of 'Other significant clinical features' can be diagnosed as incomplete KD, if other diseases are ruled out.

e: Incomplete KD may also be considered in the presence of only one or two principal clinical features after excluding other diagnoses.

Table 3 Other significant demographic, clinical, echocardiographic, and laboratory features

1. Kawasaki disease may be suspected in the presence of fewer than four principal clinical features when the following findings are observed:

- Elevation of hepatic transaminases early in the course of the disease.
- Increased leukocytes in the urine sediment of an infant.
- Thrombocytosis in the convalescent phase
- Elevation of BNP or NT-pro BNP
- Mitral valve regurgitation or pericardial effusion by echocardiography
- Enlargement of the gallbladder (hydrops of gallbladder)
- Hypoalbuminemia or hyponatremia

2. If a KD patient manifests the following findings, the patient should be considered for admission of a critical care unit.

- Hemodynamically significant myocarditis
- Hypotention (shock)
- Paralytic ileus
- Decreased level of consciousness

3. Risk scores to predict intravenous immunoglobulin resistance may be applied to guide patient management. The following features are elements of the risk scores for predicting intravenous immunoglobulin resistance.

- Leukocytosis with left shift
- thrombocytopenia
- hypoalbuminemia
- hyponatremia
- hyperbilirubinemia (jaundice)
- elevation of CRP
- Age <1 year

4. Other non-specific findings which may be observed in Kawasaki Disease and should not exclude the diagnosis.

- Irritability
- Cardiovascular: abnormal extra heart sounds, electrocardiogram changes, aneurysm of peripheral arteries other than coronary (axillary etc.),
- Gastrointestinal: abdominal pain, vomiting, diarrhea
- Hematologic: increased erythrocyte sedimentation rate, anemia
- Dermatologic: micropustular rash, transverse grooves across the finger nails.
- Respiratory: cough, rhinorrhea, retropharyngeal edema, infiltrate on chest radiograph.
- Rheumatologic: pain, swelling.
- Neurologic: cerebrospinal fluid pleocytosis, seizures, facial nerve palsy, paralysis of the extremities.

BNP, brain natriuretic protein; KD, Kawasaki disease; NT-pro BNP, N terminal pro-brain natriuretic protein.

1. Mortality in the acute phase: <0.1%.
2. Recurrence rate: 3–4%; proportion of siblings' cases, 1–2%.
3. Nonsuppurative cervical lymphadenopathy (multiple hypoechoic, enlarged nodes observed on ultrasound) is less frequently encountered (approximately 65%) compared with other principal clinical features during the acute phase. Nonsuppurative cervical lymphadenopathy is observed in approximately 90% of older children and often can be the first clinical feature of KD with fever.

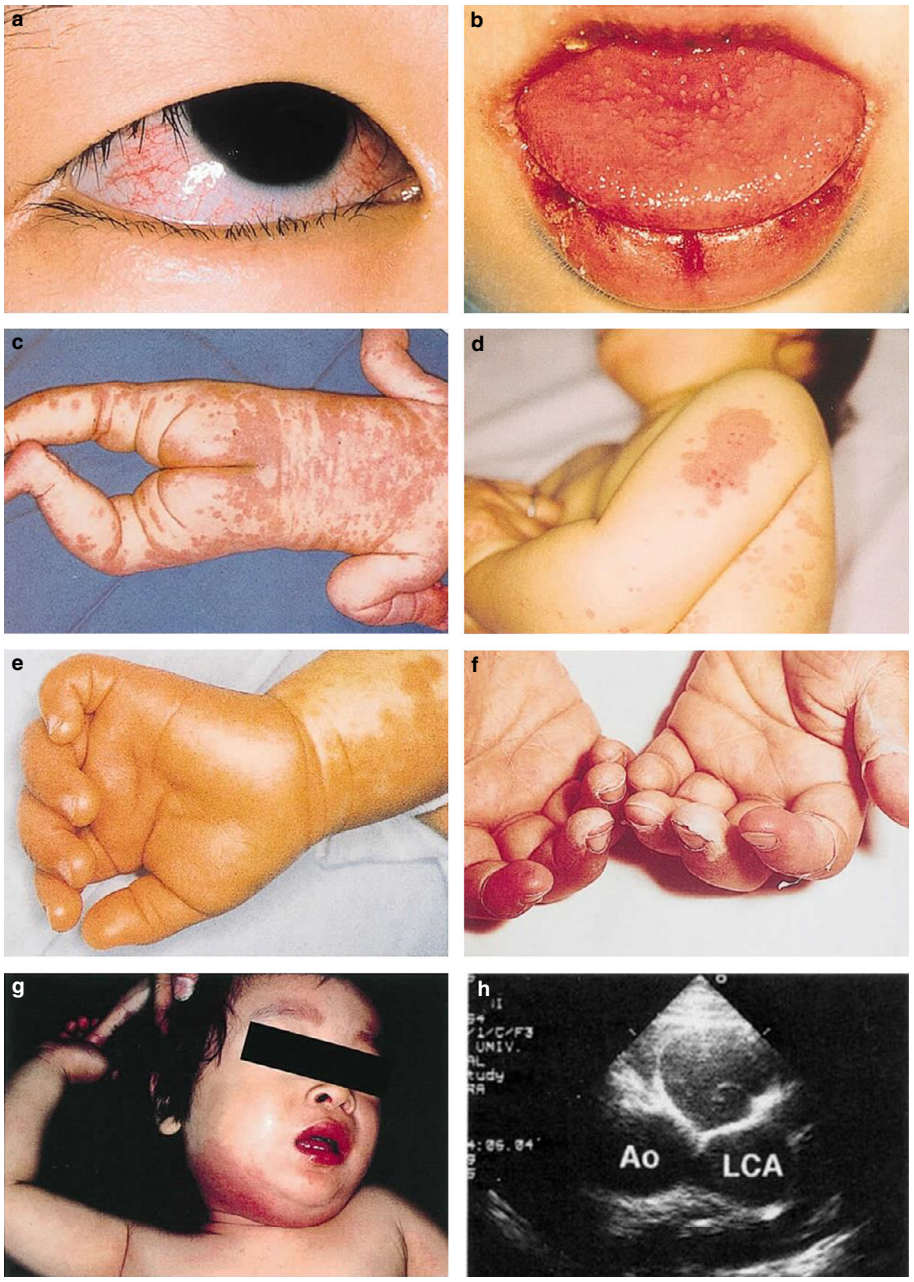

Fig. 1 (a) Bulbar conjunctival injection; (b) reddening of lips, strawberry tongue; (c) rash; (d) redness at the site of Bacille Calmette-Guèrin (BCG) inoculation; (e) reddening of palms with edema; (f) periungual desquamation; (g) non-supparative cervical lymphadenopathy; (h) Echocardiographic finding of coronary artery aneurysm.

lower than before. As we expect a continuous decrease in CALs, we modified the fever definition to reflect current practice.

2. The clinical feature of "Polymorphous exanthema" was changed to "Rash" and now includes "redness at the site of Bacille Calmette-Guèrin (BCG) inoculation". Japanese pediatricians have recognized that redness at the site of BCG inoculation is a specific clinical sign that appears at the onset of KD. In the present revision, we included redness at the site of BCG inoculation as a clinical feature that counts as "rash," even in the absence of more diffuse dermatologic changes.

In particular, this sign is observed in more than 70% of the patients whose ages are from 6 to 20 months old[3]. When the patient do not show polymorphous exanthema but shows the redness of BCG scar and other 4 principle sign, that patient can be diagnosed as not incomplete KD, but (complete) KD.

The impact of this change to the principal diagnostic clinical features will require further study and should be monitored.

3. Non-suppurative cervical lymphadenopathy (multiple hypoechoic, enlarged nodes observed by ultrasound) is less frequently encountered (approximately 65%) than other principal clinical features during the acute phase. Non-suppurative cervical lymphadenopathy is observed in approximately 90% of older children and often can be the first clinical feature of KD with fever. This phenomenon is described as "Remark"[1] at the last part.
4. The precise clinical definitions of complete and incomplete KD are now clearly delineated as outlined in the appendix and are based on the number of principal clinical features and the presence of coronary artery abnormalities. A patient who fulfills the criteria in "a" or "b" is diagnosed as complete KD. A patient who has three principal clinical features with coronary artery abnormality by echocardiography and in whom other febrile illnesses have been excluded fulfills the criteria in "c" and is diagnosed as incomplete KD. Patients who fulfill the criteria in "d" are also diagnosed as incomplete Kawasaki disease defined as the presence of three or four principal clinical features without coronary artery dilation but with features from the list of "Other significant clinical features".

Incomplete Kawasaki disease may also be considered in the presence of only one or two principal clinical features after very careful, sufficient observation and excluding other diagnoses. For these patients, particularly careful consideration of the differential diagnosis is essential. For reference, in the 24th nationwide survey, 0.7% and 5.4% of all KD patients were reported as incomplete KD with only one or two clinical features, respectively.

However, the possibilities of other disease are higher than for incomplete KD, if the coronary artery is not involved and the principal signs are limited to less than two.

Evaluation of the coronary arteries using Z scores

The revised guidelines recommend the use of Z scores for defining coronary artery dilation. When Z-score of internal coronary artery diameter ≥2.5 SD units, it is defined as coronary artery dilation. However, in case that the examiner has a difficulty to use Z score, conventional criteria using traditional measurements of inner diameter ≥3 mm (<5 years old) or ≥4 mm (≥5 years old) can be used for the diagnosis of coronary artery dilation. While Z scores are a more quantitative assessment, we realize that they have not been adopted by all centers in Japan. This change of definition may affect the incidence of coronary artery dilation, especially transient dilation and small aneurysm. Assessment of the impact of this change will therefore be important in future epidemiologic surveys.

Other significant demographic, clinical, echocardiographic, and laboratory features

In this section, we substantially revised the description of specific clinical features that can be associated with KD.

1. Seven clinical features are described that may be helpful in the recognition of incomplete KD cases. We hope that future clinical research will provide more accurate diagnostic tools including the optimum cut-off values for these variables. Although it is expected that the quantitative cut-off values of all findings in these items will be determined, there have been very few Japanese studies of sufficient quality. In the future, an algorithm using such cut-off values is expected to be constructed.
2. Clinical findings that warrant referral to a tertiary medical center with experience in treating critically ill pediatric patients are outlined.
3. Risk scores to predict intravenous immunoglobulin resistance may be applied to guide patient management. We defined seven features that are elements of risk scores predicting intravenous immunoglobulin resistance. These features may be useful in risk stratification of patients.
4. Other non-specific findings that may be observed in KD and should not exclude the diagnosis have been added. These eight features may support the diagnosis of KD.

This summary describes the major changes to the 6th revised edition of the KD diagnostic guidelines. We hope that this revision will lead to standardization of the definition of incomplete KD and diagnostic approaches, and will further reduce number of coronary artery lesions suffered by KD patients.

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Disclosure

The authors declare no conflict of interest.

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