ECG ABNORMALITIES IN KAWASAKI DISEASE AND THEIR VALUE IN PREDICTING CORONARY ARTERY ANEURYSMS

T M Hiew, H K Cheng

ABSTRACT
ECG abnormalities suggestive of carditis were encountered in 20 of 25 patients (80%) with Kawasaki Disease. The commonest abnormalities were raised S-T segments (11 patients), increased Q/R ratio (11 patients) and prolonged corrected Q-T interval (7 patients). Six patients had coronary artery dilatation and all resolved on subsequent 2-D Echocardiography. These six patients all had ECG changes of carditis. Such changes were present in 74% of patients with normal coronary arteries. The differences were not significant. A similar comparison between the two groups using the modified Asai scoring system failed to show the usefulness of this scoring system in predicting the risk of coronary artery involvement in our patients.

Keywords: Kawasaki Disease, coronary artery dilatation, carditis, Asai scoring system.

INTRODUCTION
When Kawasaki described the Mucocutaneous Lymph Node Syndrome in 1967, it was thought to be a benign and self-limiting febrile illness of children. With the recognition of this syndrome as a common entity in the paediatric population, more features of the disease became known; eg its association with aseptic meningitis, arthritis, hydrops of gall bladder, carditis and thromboarteritis with aneurysmal formation of the medium sized vessels especially the coronary arteries.

It has also become apparent that Kawasaki Disease is no longer the benign and self-limiting condition it was originally presumed to be. Sudden death occurs in 1.4% to 2.5% of all reported cases. Cardiac cases account for 85% of all deaths, noncardiac causes 6% and unknown causes 9% (1). Majority of the deaths (90%) occur in the 3rd or 4th week of the illness. Postmortem of the fatal cases almost invariably show coronary aneurysms with occlusion from thromboarteritis. Long-term morbidity especially acute myocardial infarction has also been reported.

Early recognition of the disease and timely treatment with intravenous gammaglobulin and aspirin has been known to reduce risk of coronary aneurysm formation. Surgery has even been suggested for certain selected patients. Detection of patients at risk of developing coronary aneurysms is therefore important to ensure close and adequate follow-up. Myocarditis in Kawasaki Disease receives little mention but it is not inconceivable that its occurrence and persistence contribute in part to the morbidity of the disease. The incidence of carditis in Kawasaki Disease has been reported to be high. Onoschi and Kato reported ECG abnormalities in almost all their cases. Medish reported an incidence of 60%, Takao 74% and Fujishige 70%. The present study was thus undertaken to evaluate a possible causal relationship between carditis as diagnosed by ECG changes and coronary aneurysm formation as well as to assess the predictive value of the Asai Score in patients with Kawasaki Disease.

METHODS AND PATIENTS
Between December 1985 to December 1989, 25 patients who fulfilled at least 5 out of 6 criteria specified by the Mucocutaneous Lymph Node Syndrome Research Committee in Japan were admitted to the Paediatric Department, Tan Tock Seng Hospital. The 6 criteria are:
1) Fever of 5 days or more duration, usually greater than 38°C and unresponsive to antibiotics treatment.
2) Bilateral conjunctival injection.
3) Changes in the lips and oral cavity, including dryness, redness and fissuring of lips, diffuse oropharyngeal erythema and strawberry tongue.
4) Changes in the peripheries and later desquamation of palms and soles.
5) Polymorphous exanthem without vesicles or crust.
6) Acute non-purulent swelling of cervical lymph nodes of 1.5cm diameter or more.

Oral aspirin at an anti-inflammatory dose of 100mg/kg/day was given upon diagnosis in the acute phase. This was subsequently reduced to an anti-thrombotic dose of 10mg/kg/day in the subacute phases.

Serial haemoglobin, leucocyte counts, erythrocyte sedimentation rate (ESR), ECG and chest X-ray (CXR) were done in the acute stages of the illness. 2-Dimensional Echocardiography (2D Echo) was done in all cases in the subacute phases of the disease (usually between 14th and 28th day of illness) by the same cardiologist. The proximal portions of the coronary arteries were examined echocardiographically in short-axis projection using a 5MHz transducer. The coronary artery diameters were measured 0.5cm to 1.0cm distal to the coronary orifice. Diffuse dilatation with vessel diameters ≥ 3mm or discrete aneurysm formation in that region were counted as evidence of coronary artery involvement. Those with coronary involvement had repeat 2D-Echo three weeks later. In such patients, low dose aspirin was continued till echocardiographic resolution of the coronary artery lesions.

ECG abnormalities were analysed and compared between those with coronary involvement and those without. Tracings were designated abnormal if there were changes compatible with myocarditis or pericarditis such as
1) Prolonged P-R interval of 0.17s or greater.
2) Prolonged corrected Q-T interval (Q-Tc) of 0.425s or greater.
3) R wave in V6 of 0.6mV or less.
4) R wave in V1 of 0.4mV or less.
5) Amplitude of P wave of 0.25mV or greater.
6) Duration of P wave of 0.08s or greater.
7) S-T segment depression of 0.1mV or greater for 0.06s or greater below the baseline.
8) S-T segment elevation of 0.2mV or greater (except for right praeapical leads).
9) T wave in V6 of 0.1mV or less (age less than 6 months), T wave in V6 of 0.2mV or less (age greater or equal to 6 months).
10) Evidence of myocardial ischaemia or infarction, i.e Q/R ratio of 0.3 or greater, increasing Q waves or ST-T changes or all three.
11) Standard criteria for left or right ventricular hypertrophy.
12) Various arrhythmias.

Clinical features and laboratory data of the two groups were similarly combined in a severity scoring system modified from that advocated by Asai (12) (Table I). Data were analysed by the chi-square or unpaired t-test wherever applicable.

Table I - Modified Asai Scoring System (17)

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
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<tbody>
<tr>
<td>Age &lt; 1</td>
<td>2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Fever(dys)</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td></td>
</tr>
<tr>
<td>Raised ESR (dys)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin &lt;10gm/dl</td>
<td></td>
</tr>
<tr>
<td>Maximum leucocyte</td>
<td></td>
</tr>
<tr>
<td>count (x10^9/L)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Cardiomegaly (CT ratio &gt;50%)</td>
<td></td>
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<tr>
<td>Abnormal ECG</td>
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Score ≥ 6 suggest increased risk of coronary aneurysms

RESULTS
Kawasaki Disease was diagnosed in 25 patients over the four-year study period. There was a definite male preponderance (17 males, 8 females). Twenty-two (88%) were Chinese and 3 (12%) were Malay. None of the other races were represented.

Six patients (18%) had coronary artery dilatation. Three patients had right coronary involvement, 2 had left coronary involvement and 1 had both.

None of the indices commonly used to predict coronary artery dilatation were useful. There was no statistical difference in terms of age, duration of fever, maximum ESR, minimum Hb, maximum leucocyte count and maximum platelet count between those with coronary involvement and those without. All patients with coronary artery dilatation were found to have ECG changes. These changes were present in 14 (74%) of patients with normal coronary arteries. The difference however is not significant. (Fisher Exact Probability test). Chest X-ray evidence of cardiomegaly was not useful as a predictor of coronary involvement (Table II).

The modified Asai scoring system was also not useful as an indicator of coronary aneurysm (Table II). Sensitivity of the score in predicting coronary involvement was 50% with a predictive value of positive test 30%. Specificity was 63% with a predictive value of negative test 80%.

Analysis of the ECG abnormalities encountered revealed

Table II - Clinical and laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Coronal dilatation (mean ±S.D.)</th>
<th>Normal Coronaries (mean ±S.D.)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>9.17 ± 7.68</td>
<td>23.84 ± 20.60</td>
<td>NS</td>
</tr>
<tr>
<td>Fever duration(dys)</td>
<td>9 ± 2.61</td>
<td>11 ± 2.89</td>
<td>NS</td>
</tr>
<tr>
<td>Max. ESR (mm/hr)</td>
<td>74.83 ± 45.53</td>
<td>84.53 ± 35.36</td>
<td>NS</td>
</tr>
<tr>
<td>Min. Hb (gm/dl)</td>
<td>9.60 ± 2.08</td>
<td>10.39 ± 2.05</td>
<td>NS</td>
</tr>
<tr>
<td>Max. WBC counts (mm^3)</td>
<td>24000 ± 12940</td>
<td>19490 ± 4000</td>
<td>NS</td>
</tr>
<tr>
<td>Max. platelets</td>
<td>684.17 ± 327.15</td>
<td>609.11 ± 240.04</td>
<td>NS</td>
</tr>
<tr>
<td>Number with ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Number with CT ratio &gt; 50% or CXR</td>
<td></td>
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</table>

Table III - Modified Asai Score for predicting coronary aneurysm in 25 patients with Kawasaki Disease

<table>
<thead>
<tr>
<th>Scores</th>
<th>Coronal dilatation</th>
<th>Normal Coronaries</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6</td>
<td>3</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>≤ 5</td>
<td>3</td>
<td>12</td>
<td>15</td>
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DISCUSSION
Kawasaki Disease has aroused intense interest because of its catastrophic sequelae - coronary arteritis associated with aneurysms and thrombosis, which may lead to ischaemic heart disease, arrhythmias or sudden death. Although this disease was first described in 1967, a review of the literature published prior to this showed a few reports of patients with localized aneurysms of the coronary arteries (19-21). Kawasaki Disease was not suspected as it has yet to be described; but the clinical presentation and laboratory indices of these patients bear a strong resemblance to this condition.

The incidence of coronary artery aneurysm formation in Kawasaki Disease has been variably reported from 12% to 20% (19,22-28,29). Our incidence of 18% compares similarly to those reported. The involvement of the coronary arteries in Kawasaki disease plays an important role in determining the morbidity and mortality in a condition some initially considered to be self-limiting and benign. Deaths are invariably due to cardiac involvement (20,29). Post-mortem studies often show
ECC on admission

![ECG on admission](image)

ECC Neo peeks later

![ECC Neo peeks later](image)

ECG two weeks later

![ECG two weeks later](image)

*Eg 1: 15-month-old Chinese boy with dilated right coronary artery on 2-D Echocardiography. ECG done during second week of illness showed raised S-T segment in lead II and Q in lead III. A repeat ECG two weeks later showed persistence of the findings. Patient subsequently defaulted follow-up. Cardiac enzymes were not done.*

...thromboarteritis of the coronary arteries, although involvement of the axillary, femoral and iliac arteries have also been reported (5,59). Other findings may include rupture of the coronary aneurysms, severe mitral incompetence and inflammation of the AV conduction system (5,50).

The most accepted, reliable and accurate means of diagnosing coronary aneurysm is coronary angiography (5,52,53) but unfortunately this suffers from being an invasive procedure. 2D-Echocardiography was first used by Weyman (27) to visualise the left main coronary artery and since then has been advocated for assessing coronary arterial involvement in Kawasaki Disease (9,31,38). However, it must be borne in mind that although 2D-Echocardiography is a simple and non-invasive procedure, it is not fail proof. Difficulties in visualising the coronary arteries in normal subjects have been reported (28,51,52) as well as false positive results (52,53).

Bearing the fallibility of 2-D Echocardiography as a diagnostic tool for coronary aneurysm in mind, the recognition of factors predisposing to coronary involvement become even more important. If a patient can be identified to be at risk, then conceivably, repeat 2-D echocardiography or even coronary angiography may have to be considered. Daniels (28) reported that patients with coronary involvement tend to have a longer duration of fever and a lower minimum haemoglobin concentration. Koren (27) found that the severity and duration of fever as well as the Asai score was predictive whereas others (28,30) found that only age was useful; the younger being more prone.
In our patients, none of the usual indices known or postulated to be related to an increased risk of developing coronary aneurysms were useful. Age, sex, duration or severity of fever were not useful indicators. Similarly the common laboratory indices of inflammation ie maximum ESR, maximum leucocyte counts, minimum haemoglobin counts and maximum platelet counts were not predictive. Perhaps our results suffer from the restriction of too small a sample size but it is also clear from the conflicting data published by others that it is likely that no single index can be used as a sole predictor of coronary artery involvement. The Asai score was formulated to overcome this but unfortunately, it does not appear to be useful either in our series. Furthermore, it is a retrospective scoring system and is in no way useful during the acute phases of the illness. At present, efforts are ongoing in our department to accumulate further data on subsequent admissions and perhaps with a larger population base in the future, we might be in a better position to re-evaluate the risk factors associated with coronary aneurysms.

Because so much work has been focused on assessing the coronary arteries in Kawasaki Disease, the role that myocarditis play in the disease has received less attention. It is now increasingly realised, from detailed morphological studies of the heart at necropsy, that many death cases may be related to a generalised myocarditis which may involve the A-V Conduction system as well. Yutani found from right ventricular endomyocardial biopsies that all 50 of his patients showed myocardial architecture disorganisation with hypertrophy and
inflammatory cell infiltration. Fujiwara (10) from post-mortem studies reported 9 out of 10 deaths have lesions involving the AV conduction system.

This would appear to indicate that the presence of myocardial involvement in a patient may be just as important as coronary artery involvement. 80% of our patients exhibited ECG changes compatible with carditis. This high incidence is similar to those reported by other authors (3, 19-20). We also found that a large proportion of the abnormalities in our patients reflect transmural myocardial ischaemia ie S-T segment changes and deep Q waves (Eg 1 and 2). In those patients who returned for follow-up, a repeat ECG one-month after the acute episode showed these changes to be transient. Unfortunately, because not all patients came back for review we were unable to ascertain if this was true for all the patients. Such ischaemic changes in the paediatric population are uncommon and may be seen in conditions like glycogen storage disease, myocarditis, aberrant origin of the coronary arteries, medial necrosis of the coronary arteries, and endocardial fibroelastosis (19). Unfortunately, because these changes are non-specific and may be seen in both myocarditis and ischemia from coronary arteritis, they are unlikely to be useful predictors of aneurysm formation as a large proportion of patients with Kawasaki disease show ECG changes of myocarditis. Abnormal Q waves were also encountered fairly frequently in our patients. Fujiwara (41) in a correlative study of abnormal Q waves and pathological findings in 15 patients with Kawasaki Disease, found that abnormal Q waves almost always reflect myocardial damage in over 30% of the wall thickness of the left ventricle. Abnormal Q waves may also be the only clue to the presence of asymptomatic myocardial infarction in paediatric patients (20).

Kato has also reported that prolonged Q-Tc intervals is fairly common during the acute phase of the disease (21-22). We found this to be true in our patients (Eg 3). The Q-T interval is a reflection of the total electrical systole of the ventricles and is dependent on the age and heart rate (23-24). Controversy surrounds the significance of this interval and a prolonged Q-T interval has been reported in hypertension, heart failure, electrolyte disturbances, myocarditis, pericarditis and quinidine administration (25, 26). The prolongation of this interval in some of our patients may be the result of carditis.

Viewed in this light, ECG changes in Kawasaki Disease ought to be taken seriously. Similarly, because 2D Echocardiography cannot be absolutely reliable (22, 23, 25, 26) in the detection of coronary aneurysms, if it can be established that patients with carditis, as an extension of the same inflammatory process, are at an increased risk of developing coronary aneurysms, then such patients may need to be examined more thoroughly whether by echocardiography or angiography.

M-mode echocardiography has been advocated to be a more reliable indicator of myocardial injury by Chung (30, 31) and Hirashi (32). Non-invasive thallium-201 emission computed tomography as a means to detect reversible and persistent myocardial perfusion defects and to document improvement.

**Fig 3: 6-year-old boy with normal coronaries on 2-D echocardiography. QTc intervals were measured in those leads where T waves were most distinct. Average QTc was 0.482s. No repeat ECG was done.**
with treatment has also been suggested [10,11]. With the current improved diagnostic techniques, we can expect to diagnose more young patients presenting with acute myocardial infarction complicating Kawasaki Disease.

Although all our patients with coronary aneurysms exhibited ECG changes compatible with carditis, such changes were similarly present in a significantly large proportion of those with normal coronaries. We found no correlation between carditis as diagnosed on ECG and coronary aneurysm formation. Hiroshi CHI who used both clinical and laboratory indices of carditis similarly found no such correlation.

Although we could not use these ECG abnormalities as a predictor of coronary aneurysm formation, we felt that nevertheless, it is important to identify such patients for closer follow-up in view of possible myocardial injury.

References