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Review

Differentiation between Lymph-Node-First Presentation of Kawasaki Disease from Bacterial Cervical Lymphadenitis

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Abstract

Kawasaki disease (KD) is the leading cause of acquired heart disease in children. If the patients are left untreated, coronary artery aneurysms may occur. Among the major criteria for KD, lymphadenopathy is the least common. Thus, lymph node-first presentation KD (NFKD) may be overlooked, resulting in coronary artery dilatation. Pediatric patients with fever and cervical lymphadenopathy should be cautiously evaluated for an accurate diagnosis and to minimize complications. Laboratory findings and imaging studies may help make a diagnosis in these patients. We discussed eight previous studies and compared the results of laboratory and imaging findings to differentiate between NFKD from bacterial cervical lymphadenitis (BCL).

Keywords: Kawasaki Disease; Mucocutaneous Lymph Node Syndrome; Lymphadenitis; Lymphadenopathy; Child

Introduction

Cervical lymphadenopathy is a common childhood condition, affecting up to 62% of patients aged three weeks to 6 months and over 90% of those aged 4 to 8 years old [1,2]. When lymph nodes become inflamed and enlarged, often accompanied by tenderness and redness, it is referred to as lymphadenitis [3]. Bacterial infections, including S. aureus, Group A Streptococcus, and Group B Streptococcus, are the most common cause of acute unilateral cervical lymphadenitis in young children under the age of 5, and approximately one-quarter of them may develop an abscess4). While viral lymphadenitis usually resolves on its own, treatment for bacterial cervical lymphadenitis requires appropriate antibiotics.

Kawasaki disease (KD) is an acute febrile illness caused by inflammation of the small- to medium-sized vessels of the body [5,6]. Coronary artery aneurysms occur in approximately a quarter of patients who do not receive the treatment [7]. KD is one of the most common causes of acquired cardiac disease in children, particularly in developed countries [8]. It is usually diagnosed according to the American Heart Association (AHA) guidelines based on the patient's clinical symptoms and supporting laboratory findings [9]. The criteria are comprised of clinical manifestations of systemic vasculitis. As clinical criteria are used for diagnosis, challenging subsets of patients may not fulfill the classic KD criteria [7,9]. However, a delayed diagnosis can be linked to the onset of coronary artery abnormalities [10]. Of all the criteria, cervical lymphadenopathy

is the least frequently observed symptom, with reports ranging from 50–75% of KD cases in Japan [11] to 42%–52% in the United States [12–14]. KD patients who initially present with cervical lymphadenitis, known as node-first KD (NFKD), occur in 9%–23% of KD patients [15]. NFKD can be often misdiagnosed with bacterial cervical lymphadenitis (BCL). Misdiagnosis can cause deleterious effects on the coronary arteries [14,16]. Herein, the clinical distinctions between NFKD and BCL will be reviewed so as not to delay the diagnosis and allow the occurrence of fewer complications.

Main Subject

The articles are written based on the results of searching PubMed and Google Scholar with the keywords of "Kawasaki disease" and "Cervical lymphadenitis" (Supplementary Fig. 1).

1. Clinical characteristics

The clinical characteristics of NFKD and BCL patients are presented in Table 1. The mean age at the time of diagnosis is reported as 36.0–79.2 months for NFKD and 19.2–73.1 months

Table 1. Clinical characteristics of NFKD and BCL patients in previous reports

Variables	Author	NFKD		BCL		*P* value	Reference
Age (months)	Kanegaye et al.	50.4 (32.4–64.8)	(n = 57)	19.2 (12.0–58.8)	(n = 78)	< 0.01	[14]
	Lee et al.	36.0 (0–60)	(n = 28)	46.8 (0–60)	(n = 28)	0.020	[17]
	Hwang et al.	46.6 ± 26.2	(n = 34)	50.9 ± 35.5	(n = 45)	≥ 0.05	[18]
	Nozaki et al.	48.8 ± 22.4	(n = 25)	46.4 ± 41.3	(n = 25)	0.31	[19]
	Kato et al.	55.2 (7.2–120)	(n = 12)				[20]
	Yanagi et al.	79.2 ± 27.6	(n = 14)	57.6 ± 54.0	(n = 24)	0.022	[21]
	Qin et al.	46.4 ± 22.3	(n = 47)	47.9 ± 18.2	(n = 56)		[22]
	Park et al.	47.2 ± 19.54	(n = 51)	73.1 ± 48.5	(n = 63)	0.038	[23]
	Muto et al.	34.8 (2.4–103.2)	(n = 35)	52.8 (12.0–188.4)	(n = 14)	0.20	[24]
Sex, male (%)	Kanegaye et al.	54	(n = 57)	54	(n = 78)	0.7	[14]
	Lee et al.	64.2	(n = 28)	67.9	(n = 28)	0.677	[17]
	Hwang et al.	73.5	(n = 34)	57.8	(n = 45)	> 0.05	[18]
	Nozaki et al.	72	(n = 25)	60	(n = 25)	0.55	[19]
	Kato et al.	83.3	(n = 12)				[20]
	Yanagi et al.	71.4	(n = 14)	66.7	(n = 24)	n.s.	[21]
	Qin et al.	63.8	(n = 47)	51.2	(n = 56)		[22]
	Park et al.	59	(n = 51)	54	(n = 63)	0.603	[23]
	Muto et al.	45.7	(n = 35)	42.8	(n = 14)	0.86	[24]
Duration of fever before admission (days)	Kanegaye et al.	2 (1–3)	(n = 57)	2 (1–3)	(n = 78)	0.2	[14]
	Lee et al.	4.0 (1–8)	(n = 28)	3.1 (1–5)	(n = 28)	0.133	[17]
	Hwang et al.	4.1 ± 1.4	(n = 34)	5.4 ± 1.5	(n = 45)	< 0.05	[18]
	Kato et al.	4.1	(n = 12)				[20]
	Yanagi et al.	5.0 ± 1.1	(n = 14)				[21]
	Qin et al.	5.5 ± 1.3	(n = 47)	4.3 ± 1.4	(n = 56)	< 0.01	[22]
	Park et al.	5.9 ± 1.5	(n = 51)	3.9 ± 3.3	(n =63)	< 0.001	[23]

NFKD: node-first presentation of Kawasaki disease; BCL: bacterial cervical lymphadenitis.

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for BCL [14,17–24]. There was no definite trend in the studies in which the disease group was older. In all disease groups, cervical lymphadenopathy occurred more frequently in male patients. The duration of fever before admission in the NFKD group was reported to be 2–7.7 days [14,17–23]. In two reports [14,17], the percentage of preadmission antibiotic use was 53.6%–83% and 39.3%–77% in the NFKD and BCL groups, respectively. The durations of preadmission antibiotic therapy in the NFKD and BCL groups were reported to be 1.8–2 days and 1–2.3 days, respectively. The inpatient antibiotic therapy duration in NFKD and BCL were 0–2.1 days and 2.5–4.3 days, respectively.

2. Laboratory values at initial presentation

Overall, eight previous studies reported laboratory values for NFKD [14,17–18,20–24]. A summary of previous reports is shown in Table 2. The white blood cell (WBC) count of the NFKD group was larger than that of the BCL group in four studies [17,18,21,24]. Only Kanegaye et al. and Qin et al. reported that the opposite result of WBC count in both groups [14,22]. The absolute neutrophil count (ANC) was larger in NFKD in five studies [17,18,21,23,24]. A study by Kanegaye et al. reported no significant difference in ANC in both groups, although the absolute band count was larger in the NFKD group [14]. Hemoglobin levels in the NFKD group were lower than those in the BCL group in 3 studies [14,22,23]. A difference in platelet count was reported in two studies [14,23], although the results were conflicting. Inflammatory markers and liver function tests were usually higher in the NFKD group. Interleukin-6 (IL-6) was reported in a study by Qin et al. as 121.6 pg/mL in NFKD, which was much higher than that in BCL [22]. Kidney function tests, such as creatinine and BUN, were reported in only one study [18], and there was no significant difference between the groups. Cardiac markers, including NT pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP), were significantly higher in the NFKD group [18,24].

Table 2. The mean laboratory values at initial presentation in patients with NFKD and BCL

Variables	NFKD		BCL		*P* value	Reference
WBC (× 10^3 cells/μL)	16.4 (12.4–18.8)	(n = 57)	19.0 (14.0–24.3)	(n = 78)	0.01	[14]
	19.3 (8.4–39.4)	(n = 28)	15.1 (4.5–29.3)	(n = 28)	0.047	[17]
	18.1 ± 6.1	(n = 34)	14.1 ± 74.5	(n = 45)	< 0.05	[18]
	13.3 (6.6–24.2)	(n = 12)				[20]
	18.0 ± 6.4	(n = 14)	12.7 ± 7.2	(n = 24)	0.043	[21]
	7.1 ± 2.7	(n = 47)	8.8 ± 2.0	(n = 56)	< 0.01	[22]
	15.7 ± 5.1	(n = 51)	14.5 ± 8.8	(n = 63)	0.384	[23]
	18.0 (9.3–35.2)	(n = 35)	13.4 (4.4–26.2)	(n = 14)	0.014	[24]
ANC (× 10^3 cells/μL)	12.5 (9.1–15.6)	(n = 57)	12.5 (8.9–16.4)	(n = 78)	0.8	[14]
	15.0 (3.4–29.7)	(n = 28)	9.6 (0.7–24.5)	(n = 28)	0.018	[17]
	14.2 ± 5.7	(n = 34)	9.2 ± 6.7	(n = 45)	< 0.05	[18]
	14.4 ± 5.6	(n = 14)	8.1 ± 5.2	(n = 24)	0.003	[21]
	0.32 ± 0.16	(n = 47)	0.52 ± 0.11	(n = 56)	< 0.01	[22]
	74.1 ± 13.5 (%)	(n = 51)	62.0 ± 18.8 (%)	(n = 63)	< 0.001	[23]
	14.4 (7.7–30.6)	(n = 35)	8.9 (2.0–12.2)	(n = 14)	0.003	[24]

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Table 2. Continued

Variables	NFKD		BCL		*P* value	Reference
Hemoglobin (g/dL)	11.5 (9.1–13.2)	(n = 28)	11.6 (10.0–14.7)	(n = 28)	0.690	[17]
	11.7 ± 1.1	(n = 34)	11.9 ± 0.9	(n = 45)	≥ 0.05	[18]
	12.6 ± 1.9	(n = 47)	13.2 ± 1.6	(n = 56)	< 0.01	[22]
	11.3 ± 0.9	(n = 51)	12.0 ± 1.1	(n = 63)	< 0.001	[23]
	11.7 (6.6–12.8)	(n = 35)	11.8 (10.5–14.7)	(n = 14)	0.15	[24]
Platelet (× 10^3 cells/μL)	383 (301–460)	(n = 57)	433 (336–558)	(n = 78)	0.02	[14]
	313 (73–685)	(n = 28)	299 (151–436)	(n = 28)	0.808	[17]
	323 ± 78	(n = 34)	310 ± 77	(n = 45)	≥ 0.05	[18]
	302 ± 113	(n = 14)	317 ± 131	(n = 24)	n.s.	[21]
	361 ± 107	(n = 51)	312 ± 129	(n = 63)	0.031	[23]
	331 (110–1,024)	(n = 35)	328 (138–598)	(n = 14)	0.82	[24]
ESR (mm/h)	79 (64–112)	(n = 57)	48 (31–69)	(n = 78)	0.0001	[14]
	69 (9–120)	(n = 28)	45 (5–120)	(n = 28)	0.001	[17]
	71.1 ± 29.8	(n = 34)	56.6 ± 31.3	(n = 45)	< 0.05	[18]
	32.2 ± 8.9	(n = 47)	26.2 ±7.9	(n = 56)	< 0.01	[22]
	67.4 ± 20.7	(n = 51)	49.4 ± 26.4	(n = 63)	< 0.001	[23]
CRP (mg/dL)	13.7 (7.1–21.8)	(n = 57)	6.1 (3.1–12.1)	(n = 78)	0.01	[14]
	10.7 (2.8–26.3)	(n = 28)	4.4 (0.4–18.7)	(n = 28)	< 0.001	[17]
	9.6 ± 5.1	(n = 34)	6.3 ± 6.6	(n = 45)	< 0.05	[18]
	10.4 (0.9–23.5)	(n = 12)				[20]
	10.6 ± 4.9	(n = 14)	5.2 ± 3.4	(n = 24)	< 0.001	[21]
	2.4 ± 0.7	(n = 47)	0.98 ± 0.05	(n = 56)	< 0.01	[22]
	9.3 ± 4.4	(n = 51)	5.8 ± 4.5	(n = 63)	< 0.001	[23]
	7.6 (1.4–17.52)	(n = 35)	4.1 (0.9–18.9)	(n = 14)	0.031	[24]
AST (IU/L)	153 (21–523)	(n = 28)	44 (20–294)	(n = 28)	0.206	[17]
	81.6 ± 150.8	(n = 34)	39.3 ± 35.7	(n = 45)	≥ 0.05	[18]
	143 ± 207	(n = 14)	31 ± 13	(n = 24)	0.018	[21]
	26.7 ± 9.5	(n = 47)	23.7 ± 8.0	(n = 56)	< 0.01	[22]
	134.3 ± 304.6	(n = 51)	37.4 ± 39.1	(n = 63)	0.028	[23]
	29 (19–1,909)	(n = 35)	27 (17–497)	(n = 14)	0.27	[24]
ALT (IU/L)	27 (19–76)	(n = 57)	15 (9–21)	(n = 78)	0.0001	[14]
	103 (7–560)	(n = 28)	35 (6–392)	(n = 28)	0.253	[17]
	84.4 ± 138.9	(n = 34)	26.8 ± 39.3	(n = 45)	≥ 0.05	[18]
	106 ± 150	(n = 14)	23 ± 17	(n = 24)	n.s.	[21]
	26.0 ± 10.5	(n = 47)	21.4 ± 6.1	(n = 56)	< 0.01	[22]
	118.7 ± 234.2	(n = 51)	24.9 ± 54.8	(n = 63)	0.007	[23]
	14 (7–839)	(n = 35)	12 (7–280)	(n = 14)	0.35	[24]
Total bilirubin (mg/dL)	0.73 (0.35–3.05)	(n = 35)	0.49 (0.21–0.97)	(n = 14)	0.003	[24]
GGT (IU/L)	29 (21–133)	(n = 57)	22 (19–24)	(n = 78)	0.047	[14]
	33.4 ± 15.5	(n = 47)	47.2 ± 18.3	(n = 56)	< 0.01	[22]
	65.0 ± 99.1	(n = 51)	20.3 ± 48.3	(n = 63)	0.004	[23]
Sodium (mEq/L)	134 (126–139)	(n = 35)	137 (130–140)	(n = 14)	0.004	[24]
Creatinine (mg/dL)	0.27 ± 0.09	(n = 34)	0.31 ± 0.13	(n = 45)	≥ 0.05	[18]
BUN (mg/dL)	7.6 ± 3.0	(n = 34)	8.7 ± 3.1	(n = 45)	≥ 0.05	[18]

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Table 2. Continued

Variables	NFKD		BCL		*P* value	Reference
LD (IU/L)	646 (399–1,219)	(n = 28)	621 (360–1,187)	(n = 28)	0.693	[17]
	685 ± 332	(n = 14)	637 ± 360	(n = 24)	n.s.	[21]
NT pro-BNP (pg/mL)	1,340.0 ± 2,505.6	(n = 34)	127.5 ± 122.0	(n = 45)	< 0.05	[18]
BNP (pg/mL)	76.8 ± 129.1	(n = 51)	26.9 ± 17.2	(n = 63)	0.231	[23]
	21.1 (2.0–206.4)	(n = 35)	8.0 (3.7–30.5)	(n = 14)	0.002	[24]

NFKD: node-first presentation of Kawasaki disease; BCL: bacterial cervical lymphadenitis; WBC: white blood cell; ANC: absolute neutrophil count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyl transpeptidase; BUN: blood urea nitrogen; LD: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide.

3. Radiographic findings in NFKD and BCL based on the modality of imaging

A comparison of the computed tomography (CT) results in both groups is shown in Table 3. Submental or mandibular LN enlargement rarely occurs [14,17,19]. Whether a clustered node is a dominant feature in NFKD was not definite because the result was opposite [14,23]. Suppuration of nodes appeared more frequently in the BCL group [14,17,19,23]. There was a higher presence of retropharyngeal edema in the NFKD group [14,17,19]. Adjacent inflammation and palatine tonsillar enlargement were not valuable for differentiating NFKD from BCL.

LNs in NFKD groups tend to appear as clustered nodes on ultrasound (US) (Table 4) [14,23]. Suppuration was more common in the BCL group [14,19]. Irregular-shaped and ill-defined margin nodes rarely occurred in the NFKD group [19]. Qin et al. [22] reported that evaluating

Table 3. Comparison between CT findings in NFKD and BCL

Radiographic finding	NFKD	BCL	*P* value	Reference
Location (%)				
Anterior cervical	55 (n = 12)	46 (n = 44)	0.3	[14]
	68 (n = 28)	57 (n = 28)	0.743	[17]
	100 (n = 14)	100 (n = 14)	1.000	[19]
Posterior triangle	27 (n = 12)	31 (n = 44)	0.3	[14]
	25 (n = 28)	36 (n = 28)	0.743	[17]
	29 (n = 14)	57 (n = 14)	0.25	[19]
Submental or mandibular	0 (n = 12)	18 (n = 44)	0.3	[14]
	7 (n = 28)	7 (n = 28)	0.743	[17]
	21 (n = 14)	36 (n = 14)	0.68	[19]
Low jugular	14 (n = 14)	79 (n = 14)	< 0.01	[19]
Others	18 (n = 12)	5 (n = 44)	0.3	[14]
Grouping of nodes (%)				
Dominant mass	46 (n = 12)	79 (n = 44)	0.05	[14]
	0 (n = 51)	33 (n = 63)	0.334	[23]
Clustered nodes	54 (n = 12)	21 (n = 44)	0.05	[14]
	100 (n = 51)	67 (n = 63)	0.334	[23]
Suppuration (%)	9 (n = 12)	72 (n = 44)	0.003	[14]
	21 (n = 28)	32 (n = 28)	0.946	[17]
	43 (n = 14)	57 (n = 14)	0.71	[19]
	25 (n = 12)			[20]
	0 (n = 51)	75 (n = 63)	0.040	[23]

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Table 3. Continued

Radiographic finding	NFKD		BCL		*P* value	Reference
Adjacent inflammation (%)	91	(n = 12)	95	(n = 44)	0.5	[14]
	75	(n = 28)	46	(n = 28)	0.835	[17]
	86	(n = 14)	79	(n = 14)	1.000	[19]
	83	(n = 12)				[20]
Retropharyngeal edema (%)	64	(n = 12)	33	(n = 44)	0.09	[14]
	64	(n = 28)	33	(n = 28)	0.686	[17]
	100	(n = 14)	29	(n = 14)	< 0.001	[19]
	33	(n = 12)				[20]
Palatine tonsillar enlargement (%)	93	(n = 28)	96	(n = 28)	0.787	[17]
	43	(n = 14)	43	(n = 14)	1.000	[19]
	33	(n = 12)				[20]

CT: computed tomography; NFKD: node-first presentation of Kawasaki disease; BCL: bacterial cervical lymphadenitis.

Table 4. Comparison between US findings in NFKD and BCL

Radiographic finding	NFKD		BCL		*P* value	Reference
Grouping of nodes (%)						
Dominant mass	17	(n = 12)	73	(n = 44)	0.05	[14]
	36	(n = 25)	68	(n = 25)	0.04	[19]
	7	(n = 51)	0	(n = 63)	0.039	[23]
Clustered nodes	83	(n = 12)	27	(n = 44)	0.05	[14]
	64	(n = 25)	32	(n = 25)	0.04	[19]
	93	(n = 51)	100	(n = 63)	0.039	[23]
Suppuration (%)	17	(n = 12)	45	(n = 44)	0.3	[14]
	4	(n = 25)	36	(n = 25)	< 0.01	[19]
Irregular shape (%)	0	(n = 25)	36	(n = 25)	< 0.01	[19]
Ill-defined margin (%)	0	(n = 25)	36	(n = 25)	< 0.01	[19]
Echogenicity (%)						
Homogeneous	88	(n = 25)	68	(n = 25)	0.17	[19]
Heterogeneous	12	(n = 25)	32	(n = 25)		[19]
Largest LN mean elasticity (kPa)	12.3 ± 2.8	(n = 47)	16.4 ± 2.5	(n = 56)	< 0.01	[22]

US: ultrasound; NFKD: node-first presentation of Kawasaki disease; BCL: bacterial cervical lymphadenitis.

lymph node stiffness using ultrasound elastography can be effective in differentiating NFKD from BCL. According to their report, patients with BCL tend to have stiffer largest LN.

Conclusion

In conclusion, laboratory variables such as inflammatory markers, liver function tests, and cardiac markers may be useful for differentiating NFKD from BCL. Especially, NT pro-BNP and BNP tends to be higher in NFKD group than in BCL group. Imaging studies such as CT and US, in addition to laboratory findings, can also help distinguish NFKD from BCL. Suppuration appears more frequently in BCL, whereas retropharyngeal edema occurs more frequently in NFKD. To avoid diagnostic delay, it is important to differentiate NFKD even if a patient

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is suspected to have BCL.

Supplementary Materials

Supplementary materials are only available online from: https://doi.org/10.59492/kd.1.1.e5

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