ARTICLES

A New Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome (MLNS) Prevailing in Japan

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ABSTRACT. What may be a new disease has been afflicting infants and young children in Japan since 1960. It is an acute, febrile, mucocutaneous condition accompanied by swelling of cervical lymph nodes (tentatively called mucocutaneous lymph node syndrome [MLNS]). It may be misdiagnosed as scarlet fever, the Stevens-Johnson syndrome, or infantile periarteritis nodosa. The disease is now known to be widely occurring all over Japan with an increasing incidence each year. More than 6,000 cases have been reported as of 1973. One to two percent of the patients reported have died suddenly of cardiac failure. All the autopsies showed infantile periarteritis nodosa-like arteritis accompanied by coronary thrombosis and aneurysm. Some of the surviving cases have been shown to have similar changes. These findings lead us to believe that this clinical picture is a new clinical entity. Recently, rickettsia-like bodies were found by electron microscopy in biopsy specimens from the skin and lymph nodes of the patients. The bodies were isolated by yolk sac culture and their pathogenicity is now under investigation. Pediatrics, 54:273, 1974, MUCOCUTANEOUS LYMPH NODE SYNDROME, PERIARTERITIS NODOSA, INFANTILE PERIARTERITIS NODOSA.

What may be a new disease has been afflicting infants and young children in Japan since around 1960. It is an acute, febrile, mucocutaneous condition accompanied by swelling of cervical lymph nodes (tentatively called mucocutaneous lymph node syndrome [MLNS]). It may be misdiagnosed as scarlet fever, the Stevens-Johnson syndrome, or infantile periarteritis nodosa.

The first report on MLNS was made by one of us (T. K.) in 1967 based on his experience of 50 cases with this condition. Since then similar cases have been successively reported throughout Japan. Four-thousand cases have been reported up to the present time.

In 1970 the Research Committee of MLNS, supported by the Ministry of Health and Welfare of the Japanese Government, was organized under the chairmanship of Dr. Fumio Kosaki to elucidate the clinical, pathologic, epidemiologic and etiologic features of the disease.

This paper mainly deals with the clinical and epidemiological aspects of MLNS.

CLINICAL ASPECTS OF MLNS

Since the first case was seen by one of us (T. K.) in January 1961, 168 cases of MLNS have been observed in the Department of Pediatrics, Japan Red Cross Medical Center by the end of December 1972. During that period four sudden deaths occurred in infants with MLNS. Autopsy was performed on three of these infants and showed infantile periarteritis nodosa-like arteritis of the coronary artery accompanied by thrombosis and aneurysm.

The major symptoms of MLNS are depicted in Table I which was prepared by the Committee in 1970 and based on the original report of Dr. Kawasaki in 1967.

The principal symptom is a fever ranging from 101 to 104 F, which lasts from one to two weeks and does not subside after treatment with antibiotics. This is accompanied by bilateral congestion of the ocular conjunctivae (color Fig. 1, B), a reddening of the lips and oral cavity, protuberance of

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TABLE I

Diag nostic Guideline of MLNS

PRINCIPAL SYMPTOMS

- Fever lasting from one to two weeks and not responding to antibiotics
- Bilateral congestion of ocular conjunctivae
- Changes of lips and oral cavity
  - Dryness, redness and fissuring of lips
  - Protruberance of tongue papillae (strawberry tongue)
  - Diffuse reddening of oral and pharyngeal mucosa
- Changes of peripheral extremities
  - Reddening of palms and soles (initial stage)
  - Indurative edema (initial stage)
- Membranous desquamation from fingertips (convalescent stage)
- Polymorphous exantheme of body trunk without vesicles or crusts
- Acute nonpurulent swelling of cervical lymph nodes of 1.5 cm or more in diameter

OTHER SIGNIFICANT SYMPTOMS OR FINDINGS

- Carditis, especially myocarditis and pericarditis
- Diarrhea
- Arthralgia or arthritis
- Proteinuria and increase of leukocytes in urine sediment
- Changes in blood tests
  - Leukocytosis with shift to the left
  - Slight decrease in erythrocyte and hemoglobin levels
- Increased ESR
- Positive CRP
- Increased α-globulin
- Negative ASLO
- Changes occasionally observed
  - Aseptic meningitis
  - Mild jaundice or slight increase of serum transaminase

are important for diagnosis in combination with those mentioned above are carditis, especially myocarditis and pericarditis, diarrhea, arthralgia or arthritis, proteinuria and increase of leukocytes in urine sediment, leukocytosis accompanied by shift to the left, slight decrease of erythrocytes and hemoglobin, increased ESR, positive CRP, increased α-globulin and negative ASLO. Aseptic meningitis and mild jaundice or slight increase in serum transaminase level are occasionally observed. Serum complement level is usually high in the initial stage.

Most of the patients are under 5 years of age and about half of them are under 2 years of age. The prognosis is usually good, but sometimes sudden death is seen in 1% to 2% due to coronary thrombosis. Electrocardiographic and other findings suggest that myocarditis may exist in about 70% of cases (color Fig. 1, E). Kusakawa recently reported (personal communication) angiocardiographic studies in two living children 3 and 5 years of age demonstrating coronary aneurysms and thrombosis with ECG evidence of a myocardial infarction pattern. These observations raised the possibility of a high incidence of heart damage occurring in survivors and made long-term follow-up studies in such children mandatory.

TREATMENT

The disease has been treated with various antibiotics including penicillin without response. Steroids may have an antifebrile effect on the disease but it is doubtful if they can reduce the duration of the disease. A key point in management is how to prevent the serious complications.

CLINICAL COURSE

An example of clinical course of the case with MLNS is illustrated in Figure 1.

The disease can clinically be differentiated from scarlet fever or Stevens-Johnson syndrome (Table II). The clinical pattern of MLNS is also different from that of periarteritis nodosa in infancy, though description of the clinical features of the latter is insufficient in the literature. It is noteworthy to mention, however, that the pathological findings in 13 autopsied cases of MLNS seem to be consistent with those of periarteritis nodosa.

EPIDEMIOLOGICAL ASPECTS OF MLNS

Two nationwide surveys on MLNS have been conducted by the Committee in 1971 and 1973 to collect and register all the cases with this disease in Japan for epidemiological analysis. The steps and the results of the surveys are outlined below.
COLOR FIG. 1. A. Typical exanthema of MLNS in a 10-month-old male infant on the fourth day of illness. B. Congestion of ocular conjunctiva in an 8-month-old female infant on the fifth day of illness. C. Desquamation at fingertips in an 18-month-old infant on the 14th day of illness. D. Erythema and indurative edema of the palm in an 11-month-old infant on the fourth day of illness. E. Thrombosis and aneurysm of bilateral coronary arteries at autopsy in a 9-month-old male infant who suddenly died on the 59th day from MLNS.
cases with MLNS in Japan, a very simplified questionnaire was sent to all the pediatric departments of hospitals with more than 100 beds (1,458 hospitals in 1971 and 1,452 in 1973), inquiring about their experience with MLNS. Diagnostic guide-

lines were prepared by the Committee and distributed with the questionnaire.

In the 1971 survey 631 hospitals returned the questionnaire. A response rate of 43% showed 415 hospitals reporting 3,140 cases up to 1970. In the 1973 survey which was intended to cover the two years, 1971 and 1972, 821 (57%) hospitals responded and 518 hospitals reported 3,098 cases.

An analysis of these data revealed that no characteristic distribution of the cases was seen geographically.

2. In order to register all the cases of MLNS individually, a simplified "individual" card was later sent to the 415 hospitals in 1971 and 518 in 1973 that had responded to the first questionnaire. In both surveys 3,940 cases were registered, including 675 suspected cases which were subjected to epidemiologic analysis by sex, age, date of onset, etc. The results obtained are listed below.

Male:female ratio, 1.5:1.

Age distribution is monomodal with a peak in the last half of the second year after birth, followed by the latter half of the first year (Fig. 2).

<table>
<thead>
<tr>
<th>TABLE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential Diagnosis of MLNS From Stevens-Johnson Syndrome and Scarlet Fever</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Under 5 years</td>
</tr>
<tr>
<td>Eyes</td>
</tr>
<tr>
<td>Lips</td>
</tr>
<tr>
<td>Oral cavity</td>
</tr>
<tr>
<td>Peripheral extremities</td>
</tr>
<tr>
<td>Indurative edema</td>
</tr>
<tr>
<td>Exanthema</td>
</tr>
<tr>
<td>Swelling of cervical lymph nodes</td>
</tr>
<tr>
<td>Genitals</td>
</tr>
<tr>
<td>Penicillin therapy</td>
</tr>
<tr>
<td>Throat culture</td>
</tr>
<tr>
<td>Seasonal variation of occurrence</td>
</tr>
<tr>
<td>Autopsy findings of coronary artery</td>
</tr>
</tbody>
</table>
TABLE III
NUMBER OF MLNS CASES REGISTERED AND CASES OF SUDDEN DEATH BY YEAR

<table>
<thead>
<tr>
<th></th>
<th>Definite</th>
<th>Suspected</th>
<th>Total</th>
<th>Sudden Fatality Death Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964 or before</td>
<td>67</td>
<td>21</td>
<td>88</td>
<td>1.1</td>
</tr>
<tr>
<td>1965</td>
<td>47</td>
<td>14</td>
<td>61</td>
<td>1.6</td>
</tr>
<tr>
<td>1966</td>
<td>57</td>
<td>22</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>1967</td>
<td>77</td>
<td>24</td>
<td>101</td>
<td>2.0</td>
</tr>
<tr>
<td>1968</td>
<td>261</td>
<td>49</td>
<td>310</td>
<td>2.6</td>
</tr>
<tr>
<td>1969</td>
<td>379</td>
<td>82</td>
<td>461</td>
<td>2.0</td>
</tr>
<tr>
<td>1970</td>
<td>700</td>
<td>187</td>
<td>887</td>
<td>1.2</td>
</tr>
<tr>
<td>1971</td>
<td>688</td>
<td>116</td>
<td>804</td>
<td>1.3</td>
</tr>
<tr>
<td>1972</td>
<td>979</td>
<td>156</td>
<td>1,135</td>
<td>1.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>4</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>3,265</td>
<td>675</td>
<td>3,940</td>
<td>65</td>
</tr>
</tbody>
</table>

Distribution according to month of onset shows a slight seasonal variation of the disease, with an increased number observed in the summer.

The occurrence of new cases has increased significantly since 1968. This is probably attributed to the increased awareness of pediatricians for this disease (Fig. 3).

No familial occurrence has been observed.

Cases of sudden death due to MLNS were and are being reported every year. A total of 65 were reported by the end of 1972. The case fatality rate per year is approximately 1.7% (average range, 0% to 2.6%) (Table III). Ninety percent of the fatal cases have been due to sudden death caused by coronary thrombosis and aneurysm.

3. To analyze the symptoms and clinical course of the cases, detailed “individual” cards were prepared for 760 randomly selected cases in 415 hospitals of the 1971 survey. Sixty percent of these cases had all the principal symptoms listed in the diagnostic guideline; one or two symptoms were lacking in the remaining cases.

Principal symptoms and frequencies of manifestation of each in these cases are as follows:

- Fever, 95%
- Congestion of conjunctivae, 88%
- Changes of lips and oral cavity
  - Dryness, redness of lips, 90%
  - Protuberance of tongue papillae, 77%
  - Reddening of oral mucosa, 90%
- Changes of peripheral extremities
  - Reddening of palms and soles, 88%
  - Indurative edema, 76%
  - Desquamation from fingertips, 94%
  - Polymorphous exanthema of body trunk, 92%
  - Swelling of cervical lymph nodes, 75%

The results of 227 throat culture specimens showed *Streptococcus* in 93 (S. viridans, 69; S. hemolyticus, 14); *Staphylococcus*, 57; *Neisseria catarhalis*, 56; *Escherichia coli*, 19; and *Candida*, 10.

The results of the following tests were negative:

- Blood culture, 47 cases; rheumatoid arthritis factor, 19 cases; complement fixation (adenovirus, mumps, coxsackievirus, polio, echovirus, herpes simplex, etc.), 27 cases; Paul-Bunnel, 36 cases; Coombs', 36 cases; lupus erythematosus cell preparation, 10 cases; and cold hemagglutination, 33 cases.

4. In order to clarify the factors related to the occurrence of MLNS, a case control study was preliminarily conducted by the matched-pair method at one hospital. In this study the medical records of 57 MLNS patients admitted to the hospital between 1968 and 1970 were investigated together with those of control patients of the same age, sex, period of admission and with other diseases.

The proportion of artificial feeding during infancy was significantly higher in the MLNS group than in the controls. This study is now in progress, and 11 hospitals are being interviewed for confirmation of the above results.

ETIOLOGY OF MLNS

The etiology of the disease has remained unknown up to the present, though various theories have been proposed. An abnormal host reaction to
any of a variety of different infections has been suggested and an allergic reaction against chemical detergents has been considered.

Recently, rickettsia-like bodies were found by electron microscopy in biopsy specimens obtained from the skin or lymph nodes of 12 of 23 patients with MLNS. The bodies were located in the cytoplasm of macrophages, of endothelial cells of arterioles, and clustered inside the vascular lumen. These bodies were isolated by yolk sac culture and their pathogenicity is now under study.

CONCLUSION

The clinical and epidemiologic features of a new infantile, acute, febrile mucocutaneous lymph node syndrome (MLNS) are reported. The disease is now confirmed to be widely occurring all over Japan with an increasing incidence each year. More than 6,000 cases have now been reported (1973).

One to two percent of the patients died suddenly of cardiac failure. All 13 autopsies showed infantile periarteritis nodosa-like arteritis accompanied by coronary thrombosis and aneurysm.

Some of the surviving patients also had similar changes associated with the heart. All these facts lead us to believe that the clinical features of the disorder constitute a new clinical entity.

Recently, rickettsia-like bodies were found by electron microscopy in biopsy specimens from the skin and lymph nodes of the patients. The bodies were isolated by yolk sac culture and their pathogenicity is now under discussion.

REFERENCES


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