ORIGINAL ARTICLE

An Outbreak of BCG Related Lymphadenitis in Malaysian Infants

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Summary

A study was done on 638 infants with BCG related lymphadenitis seen between August 1990 and December 1993. Most infants (86.5%) had developed symptoms by six months after vaccination and the nodes became suppurative in 317. Surgical procedures were carried out in 82 cases and the rest were managed conservatively. The mean duration to resolution was 6.6 months (range 1 to 29 months). This outbreak was related to a change from the Japan to the Pasteur strain of BCG. The incidence remained high (> 15 per 1000 live births) despite a dose reduction from 0.1 ml to 0.05 ml, but declined when the Japan strain was reintroduced in April 1992.

Key Words: BCG related lymphadenitis, Pasteur strain of BCG, Malaysian infants

Introduction

In Malaysia, the BCG vaccination programme has been a highly successful component of the National Tuberculosis Control Programme. Since 1961 it has been fully integrated with basic medical and health services and from 1987 the coverage for newborn infants has exceeded 98% of live births[1].

Caseating regional lymphadenitis is a recognised adverse reaction following BCG vaccination of newborn children. From August 1990 a marked rise was noted in the number of infants with this BCG related complication and the number of cases only began to decline in late 1992. Our study documents the characteristics, management and outcome of infants with BCG related lymphadenitis seen in Penang during this outbreak.

Materials and Methods

All infants with BCG related lymphadenitis seen at government medical and health facilities in Penang State between August 1990 and December 1993 were included in the study. From early 1991 all doctors, including those in the private sector, were requested to report their cases to the Chest Clinic, Penang Hospital. Data was obtained on age at immunisation, time to onset of symptoms, strain and dose of vaccine used, number and site of enlarged nodes, treatment and outcome. Infants with lymphadenitis in the left axilla and/or lower cervical region were included in the study.

Viability tests were done on samples of BCG vaccine taken at random from government hospitals and health centres throughout the state. The results of viability tests taken from 1990 until 1993 were recorded.

Results

The total number of infants studied was 638; 50 were reported between August and December 1990, 363 in 1991, 211 in 1992 and only 14 in 1993 (Table I).

The age of vaccination could be ascertained in 626 infants. In accordance with the national policy to

vaccinate as early in life as possible, 543 infants (86.7%) had received BCG vaccination by the second day after birth and 600 (95.8%) within the first two weeks of life. Among those vaccinated after the second week of life, 17 had been delivered at home, vaccination had been delayed in six on account of prematurity and the reason for delay in vaccination could not be determined in three cases.

Doctors in government chest clinics followed-up 554 infants (86.8%), 25 were seen in Paediatric, Surgical or Outpatients departments of government hospitals and another 59 were treated in health centres, maternal and child health clinics or rural health clinics.

Vaccine strain and dose

The strain of BCG used for mass vaccination under the National Tuberculosis Control Programme was changed from Japan freeze-dried to the Pasteur strain in May 1990.

The Japan strain at a dose of 0.1 ml had been in use for more than 15 years with a very low rate of complications. From May 1990 until August 1990 the Pasteur strain was administered at a dose of 0.1 ml and from September 1990 the dose for newborn infants was reduced to 0.05 ml (which is the recommended dose for infants under one year of age). The Japan strain was reintroduced in April 1992. All vaccinations during the study period were carried out by trained nurses with considerable experience in using the intradermal technique.

Among the 638 infants with BCG related lymphadenitis in this study, the vaccine strain used was Pasteur in 569 cases (89.2%), the Japan strain in 12 cases (1.9%) and unknown in 57 cases (8.9%).

An analysis was done to determine the incidence of BCG related lymphadenitis in infants born under the care of government medical and health facilities in Penang State between 1990 and 1992. This analysis did not include 77 infants born in other states and seven born under the care of private doctors. Table II shows that the Japan strain was associated with a very low incidence of this complication whereas the Pasteur strain produced a much higher incidence which persisted despite a reduction in dose from 0.1 ml to 0.05 ml. The overall incidence of BCG related lymphadenitis in infants born between May 1990 and March 1992 and vaccinated with Pasteur vaccine was 16.2 per 1000 live births.

Table I
Number of infants with BCG related lymphadenitis reported in Penang State 1990 – 1993

Time Period Cases Reported	Place of vaccination					
	Penang Island	Seberang Perai Utara	Seberang Perai Tengah	Seberang Perai Selatan	Other States	Total
Aug – Dec 1990	16	6	27	0	1	50
Jan – Dec 1991	158	61	95	11	38	363
Jan – Dec 1992	63	23	81	10	34	211
Jan – Dec 1993	3	1	6	0	4	14
TOTAL	240	91	209	21	77*	638

* *Kedah 34, Perak 23, Kelantan 4, Johor, Malacca and Selangor 3 each, Perlis and Kuala Lumpur 2 each, Sabah 1 and unknown 2*

Table II
Incidence of BCG related lymphadenitis in infants born under the care of government medical and health facilities, Penang State, February 1990 to December 1992

Time Period	No. of Live Births	Vaccine Strain and Dose	No. Who Developed BCG Related Lymphadenitis	Incidence Per 1000 Live Births
Feb – Apr 1990	4326	Japan 0.1 ml	2	0.5
May – Aug 1990	6012	Pasteur 0.1 ml	90	15.0
Sep – Dec 1990	5910	Pasteur 0.05 ml	104	17.6
Jan – Dec 1991	17274	Pasteur 0.05 ml	268	15.5
Jan – Mar 1992	4112	Pasteur 0.05 ml	77	18.7
Apr – Dec 1992	12784	Japan 0.1ml	8	0.6

Time to onset of symptoms

Data on time to onset of symptoms was available in 623 infants. Time to onset of symptoms was computed from age when the enlarged nodes were first noticed or from age at first presentation (if the parents/ guardian could not recall when the nodes first appeared) together with age at vaccination. Table III shows that 86.5% of infants had developed lymphadenitis within six months of vaccination. The median time to onset of symptoms was three months (range one week to 24 months).

Number, site and size of nodes

The number, site and size of nodes at first presentation is shown in Table IV. The majority of infants had a single left axillary node although a few had axillary and/or lower cervical nodes. One infant had both left axillary and right inguinal lymphadenopathy. Just over 10% of infants had multiple enlarged nodes. The median size of enlarged nodes at presentation was 1.5 cm in diameter. In 317 infants (49.7%) the enlarged nodes became suppurative with abscess formation and in 174 the nodes resolved without suppuration. In the remaining 147 infants it was unknown whether the nodes became suppurative or not. The mean node size at presentation in 235 infants with single nodes which became suppurative was larger than in 147 infants with single enlarged nodes which did not suppurate (size in cm (SD) 1.93 (0.95) v. 1.38 (0.77), $p<0.001$).

Management

Guidelines on the management of BCG related lymphadenitis from the National Tuberculosis Centre were circulated in June 1991 and most infants were managed conservatively, that is, without surgical intervention. Parents were reassured regarding the

condition and infants were followed-up until resolution whenever possible.

Just over 73% of patients (468) received antibiotics other than isoniazid: 344 received erythromycin (16 received more than one course), 24 received cloxacillin (one received two courses), 11 ampicillin, 67 two or more of these antibiotics and 22 received antibiotics of unknown type. The duration of each course of antibiotics was usually 10 to 14 days. One child developed rashes and another developed diarrhoea with erythromycin; no other adverse reactions to antibiotics were reported in this series. A course of isoniazid at a dose of 5 mg/kg/day was given to 156 infants (including 115 who had received other antibiotics) for an average duration of 2.3 months (range two days to eight months). In two cases the drug had to be stopped after two days because of rashes but it was otherwise well tolerated. One infant with congenital rubella syndrome who developed left axillary and inguinal lymphadenopathy, failure to thrive and hepatospenomegaly was given a full course of anti-tuberculosis treatment for presumed disseminated BCG infection with good clinical response.

In 238 infants with suppurative lymphadenitis, the nodes

Table III
Cumulative distribution of time to onset of symptoms in 623 infants with BCG related lymphadenitis

Time to onset of symptoms	1 mth	2 mths	3 mths	4 mths	5 mths	6 mths	12 mths	24 mths
Cumulative % of patients	8.3	26.8	52.2	69.0	80.1	86.5	97.8	100

Table IV
Number, site and size of enlarged nodes at presentation in 638 infants with BCG related lymphadenitis

		Site of enlarged notes				
		Axillary	Cervical	Cervical & Axillary	Inguinal & Axillary	Total
Number of nodes	1	557	14	0	0	571
	2	33	4	22	1	60
	≥ 3	2	0	5	0	7
	Total	592	18	27	1	638
Size of nodes	<1cm	82	1	14	0	97
	1-1.5cm	245	10	26	0	281
	2-2.5cm	161	5	11	0	177
	3cm	64	0	4	0	68
	≥ 4cm	15	1	1	0	17
	Unknown	63	5	6	2	76
	Total	630	22	62	2	716

fistulated and discharged spontaneously. Incision and drainage was done in 46 infants, 12 had needle aspiration of pus, one had both aspiration and incision and drainage, 22 infants had complete excision of the enlarged nodes and 1 had incision and drainage followed by excision.

There was recurrence of lymphadenitis after resolution in 10 infants. The nodes had discharged spontaneously in four infants, then recurred and resolved after a course of isoniazid. The lymph nodes recurred in three infants who had incision and drainage; one of them had repeat incision and drainage and another subsequently underwent complete excision. Another three infants had recurrent lymphadenitis after excision, and one of these infants had a repeat excision done.

Table V
Duration to resolution in infants with BCG related lymphadenitis in relationship to various patient factors

Factor	No. of Infants	Duration to Resolution (SD/months)
Time to onset of symptoms		
≤ 2 months	107	7.8(5.4)*
> 2 months	327	6.3(4.7)*
Number of nodes at presentation		
Single	400	6.2(4.6)*
Multiple	45	9.9(5.8)*
Size of node at presentation		
Single node ≤ 2 cm	286	5.9(4.3)*
Single node > 2 cm	61	8.6(6.0)*
Suppurative		
Yes	275	6.1(4.5)*
No	170	7.4(5.3)*
Isoniazid		
Yes	119	7.2(5.7)
No	326	6.4(4.6)
Antibiotics		
Yes	327	6.7(5.0)
No	118	6.3(4.6)

**Statistically significant differences, $p < 0.05$*

Outcome

Of the 638 infants, 459 were followed-up until complete resolution of the enlarged nodes. The mean duration to resolution was 6.6 months (range one to 29 months) from data available in 445 infants. The outcome was unknown in 160 infants who were lost to follow-up after a mean duration of follow-up of 3.7 months (range 0 to 23 months). Another 19 infants were still on follow-up after a mean duration of follow-up of 18.3 months (range four to 32 months) at the time the study was stopped in December 1993. Overall the mean duration of follow-up in the 638 infants was 5.9 months (range 0 to 34 months).

Table V shows the relationship between the duration to resolution of lymphadenitis and various patient factors. Duration to resolution was significantly shorter in patients with time to onset of symptoms of more than two months compared to those with shorter time to onset of symptoms. Infants with single nodes had shorter duration to resolution than those with multiple enlarged nodes. In patients with single nodes, those with nodes smaller than or equal to 2 cm in diameter at presentation had shorter duration to resolution than those with larger nodes. Those with suppurative nodes had shorter duration to resolution than infants with nodes that did not become suppurative. In most cases resolution of suppurative nodes followed soon after spontaneous discharge or surgical procedures (usually within two or three months). Infants given erythromycin or other antibiotics did not show any significant difference in duration to resolution of lymphadenitis compared to patients who had not been given antibiotics. Duration to resolution in infants given isoniazid also did not differ significantly from that in infants not given isoniazid.

Laboratory findings

Only 40 infants had bacteriological and/or histological evidence of BCG related lymphadenitis. Pus from

suppurative nodes grew mycobacteria identified as belonging to the *M. tuberculosis complex* in 19 of 83 cases (22.9%). Pus direct smear for acid fast bacilli was positive in five out of 23 cases (21.7%), three of whom also had positive pus culture for mycobacteria. Histopathological examination of nodes excised surgically from 21 infants showed tuberculous lesions and features consistent with BCG related lymphadenitis (such as caseation necrosis, epithelioid granulomata and Langhans giant cells); two of these infants also had positive pus culture for mycobacteria.

Culture of pus for bacterial pathogens from 73 infants yielded staphylococci in 53 instances, gram-negative rods in five and β haemolytic streptococci in one infant.

Viability tests

All viability tests on samples of Japan freeze-dried vaccine showed satisfactory counts quoted as more than 15 million viable units/ml (vU/ml). For example, eight samples tested between January and April 1990 cultured an average of 39.9 million vU/ml. The recommended viability counts for Pasteur vaccine was two to 4.8 million vU/ml, but viability tests on random vaccine samples showed highly variable results. Between May 1990 and March 1992, 60 samples of Pasteur vaccine were sent for viability testing and only 16 out of the 60 results fell within the 'satisfactory' range. In two samples the vaccine potency was slightly below the 'satisfactory' range and the remaining 42 samples cultured greater than the upper recommended upper limit of 4.8 million vU/ml. In 34 samples the result was between 4.8 and 10 million vU/ml, 4 samples cultured between 10 and 30 million vU/ml and 4 had viability counts of between 30 and 40 million vU/ml.

Discussion

Bacillus Calmette Guérin was developed by attenuating an original virulent strain of *Mycobacterium bovis* by more than 200 subcultures over many years[2,3]. It has been used to prevent tuberculosis since 1921 and from 1950 has played an important role in tuberculosis control programmes throughout the world. BCG has been shown not to prevent establishment of infection but protects by limiting the spread of tubercle bacilli. Its protective efficacy varies from 60 to 90% for prevention of rapidly developing disseminated disease (miliary tuberculosis or meningitis) in young children[4]. In Malaysia, the vaccination policy is primary vaccination at birth with one revaccination during childhood (primary school leavers), and the BCG vaccination programme has been integrated into the World Health Organization's Expanded Programme on Immunisation.

The adverse effects of BCG vaccine have been extensively studied[5,6]. Complications can occur at the site of injection, in the regional lymph nodes or following dissemination of bacilli. Local and regional reactions include persistent ulceration, abscesses, suppurative or non-suppurative lymphadenitis, keloid scars and lupoid reactions. More serious reactions include metastatic abscesses, osteitis, multiple lymphadenitis, hepatosplenomegaly and rare disseminated BCG infections.

Lymphadenitis following BCG vaccination is the most frequent adverse reaction encountered and suppurative lymphadenitis has been reported in 0.1 to 4% of immunised children under two years of age[5,6]. It has been stated that minor degrees of lymph node enlargement which subside spontaneously are an exaggeration of the normal course of vaccination and should not be considered as adverse reactions to BCG. In this study there was difficulty in distinguishing simple hypertrophic nodes from suppurative lymphadenitis. No cases were excluded based on node size at presentation because it became apparent that even nodes as small as 0.25 cm in diameter at presentation could eventually enlarge and suppurate. Follow-up data revealed that the mean duration to resolution was longer in infants with non-suppurative nodes than infants with suppurative nodes. Furthermore, some non-suppurative nodes were as large as 5 cm in diameter at presentation and in 12 cases, surgical excision of non-suppurative nodes had to be resorted to because of failure to resolve on conservative management. Hence we felt it was unjustified to exclude infants with non-suppurative nodes from this study. During this outbreak, 1 to 2% of newborn infants immunised with BCG developed BCG related lymphadenitis. This incidence is likely to be an underestimate since some infants may have been treated by private doctors or treated in other states and not notified to our clinic.

For future surveillance of BCG adverse reactions, it would be desirable to provide clear guidelines to define abnormal lymphadenopathy following BCG vaccination. Temporary enlargement of regional lymph nodes which resolves without suppuration can be excluded hence criteria should be set for size of nodes and duration of lymphadenopathy so that a standard case definition can be used for case-finding by health care workers.

As in other studies, most cases occurred within six months of vaccination[5-8], although the onset of symptoms was delayed beyond 12 months in a small percentage of cases. There was bacteriological and/or histological confirmation in only 6.3% of cases because the occurrence of lymphadenitis was clearly related to BCG and tests were not routinely done to substantiate all cases.

BCG related lymphadenitis is usually a benign and self limiting condition[9,10] but spontaneous resolution may take many weeks or months. The management of these lesions has been much debated. Some authors have recommended total surgical excision of suppurative nodes (with or without anti-tuberculosis therapy) to hasten healing and to prevent the occurrence of persistent draining sinuses[11-15]. There has been disagreement with this approach on the grounds that it may adversely affect the acceptability of the immunisation policy in infants[16]. Isoniazid has been advocated to prevent suppuration or to expedite healing after surgical incision or spontaneous discharge[10,17]. Erythromycin has also been reported to be useful for the treatment of troublesome BCG lesions such as cold abscesses and persistent ulceration at the site of vaccination[18,19]. Although some atypical mycobacteria have been shown to be sensitive to erythromycin *in vitro*, the minimal inhibitory concentration of erythromycin for the BCG organism has been found to be much higher than that produced by oral administration of the drug[20]. One study on patients with BCG related lymphadenitis has reported that isoniazid does not shorten duration to resolution[15] and another has demonstrated that neither isoniazid nor erythromycin has any effect in preventing suppuration[21]. In our study neither antibiotics (mainly erythromycin) nor isoniazid was found to have any effect on the natural resolution of the enlarged nodes. More studies are needed to determine whether either erythromycin or isoniazid is useful in the treatment of BCG related lymphadenitis. We feel that infants with this complication of BCG vaccination should be managed conservatively and surgical excision should be reserved for persistent swollen or draining glands. This is particularly so since six of 82 infants who had surgical procedures suffered recurrence of lymphadenopathy after surgery. It would be reasonable to prescribe a short course of either erythromycin or isoniazid since parents often expect some form of treatment and these drugs rarely cause side-effects.

One infant in this series was felt to have disseminated BCG infection which is usually related to a severe or partial defect in cell-mediated immunity[5,22]. She had congenital rubella which can give rise to humoral and/or cellular immunodeficiency, and BCG infection was confirmed from bacteriological and histological examination of an excised left axillary node. She made a good recovery after a full course of anti-tuberculosis therapy.

Complications of BCG vaccination are often related to the strain and dose of BCG used, the age of the child and the skill of staff performing intradermal vaccination[2,7,9]. The risk of local complications due to an overdose or too deep an injection is higher in newborns than in older children[5]. At present BCG is available in the form of several substrains from various laboratories which differ in residual virulence (level of attenuation)[2]. Many outbreaks of BCG related lymphadenitis have occurred in other countries following a change in vaccine strain from a more to a less attenuated vaccine strain, most often to the more reactogenic Pasteur strain[4,22]. The vaccine potency (expressed as viable Units/ml) has also been found to affect the risk of BCG related lymphadenitis. In general more reactogenic vaccines have lower numbers of culturable particles per dose[4]. Reducing the total injected dose of BCG (number of viable Units/dose) has been shown to decrease the incidence of BCG related lymphadenitis[5,6,23], and one study has suggested that the dose of Pasteur vaccine for infants should be reduced to a quarter dose (0.025 mg) in order to avoid the occurrence of this complication[24].

There is little doubt that imprecise vaccination

technique can contribute to local complications. Vaccinators who are used to a vaccine of lower potency with virtually no complications may be less cautious with overdosage or subcutaneous injection[9] and if this imprecise technique is used following a change in vaccine strain for a more potent vaccine, the risk of complications will increase. Since reducing the dose from 0.1 ml to 0.05 ml or half strength dilution of vaccine can present technical difficulty for vaccinators, an alternative strategy which has been suggested is control of the viability of vaccine batches expressed as viable Units/ml (with 95% confidence limits) to ensure that the vaccine used is of a uniform quality[2]. The dose can be calibrated to bring down the complication rate without reducing the protective effect[7,9]. In our study, reducing the dose of Pasteur vaccine from 0.1 ml to 0.05 ml did not reduce the rate of BCG related lymphadenitis. This may be related to the wide variation in vaccine potency between batches of vaccine. Some batches of high potency cultured up to seven to eight times the upper limit of recommended viability counts.

The underlying causes of adverse events following immunisation need to be identified and corrected. If the incidence of postvaccination regional lymphadenitis rises above 1%, this can adversely affect the acceptability of immunisation services[4]. The sudden outbreak of BCG related lymphadenitis in Malaysia caused concern among the public and within the medical profession. It was highlighted in the press in 1991[25-27] and again in 1993[28-30].

Conclusion

This study describes the first major outbreak of BCG related lymphadenitis in Malaysia. The outbreak was related to a change in the vaccine strain from the Japan to the Pasteur strain of BCG in May 1990. Following the reintroduction of the Japan strain in April 1992, the incidence of this complication has declined to its previous low level.

Changes in the strain of BCG vaccine used for mass vaccination of newborn children should be avoided to prevent this complication which can adversely affect the national immunisation programme.

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