INTERSTITIAL MONONUCLEAR PNEUMONIA

A Cause of Sudden Death in Gurkha Infants in the Far East

BY

the late J. D. CRUICKSHANK, A. P. TRIMBLE and J. A. H. BROWN
From the Medical Directorate, Far East Land Forces, Singapore

(RECEIVED FOR PUBLICATION FEBRUARY 28, 1957)

For the past few years interstitial mononuclear pneumonia has been recognized as a cause of sudden death in infancy in America and elsewhere (Grunwald and Jacobi, 1951). The following report is a result of an investigation prompted by the occurrence over some years of cases of sudden or rapid death in Gurkha infants in Malaya and Hong Kong for which a completely satisfactory explanation was lacking. Many had been classified as bronchopneumonia although the pathological findings were not typical. On religious grounds permission for post-mortem examination was often refused and diagnosis was made on clinical grounds which again were often atypical. Accurate clinical descriptions were scanty when death occurred in isolated stations, and indeed at the beginning of the investigation it was by no means certain that a primary respiratory infection was the cause.

Material

The 18 cases described here were all proved histologically at necropsy. They were derived from the re-investigation of past fatal cases of which notes and pathological material were available (Cases 1—7), and from a series of 58 patients with fulminating respiratory infections of whom 32 died; permission for post-mortem examination was obtained in 19 cases (Cases 8—18).

Clinical Description

The clinical histories are summarized in Appendix I. The ages of the babies varied from 1 to 7 months, averaging 3 months. Ten of the 18 cases were aged 2 months or under. There was no seasonal incidence and the cases were for the most part sporadic over a wide area with the exception of one period when two cases were admitted to one hospital in one month and a further two cases within the next three months (Cases 1—4). The previous health of both the mothers and the children was, to outward appearances, usually excellent.

Immediately preceding illness of a mild character for one or two days occurred in nine cases before the acute respiratory symptoms appeared or the baby was found dead in bed. These were most often mild diarrhoea or mild ‘feeding problems’. Two cases gave a history of respiratory illness.

Three babies were found dead in bed and a fourth died on being picked up. The rapidity of the process was the outstanding feature in all the other cases. This varied from under one hour to a maximum of 36 hours. The change to an obviously very serious condition was always extremely rapid and at times could be described as sudden. Collapse was a prominent feature and there was respiratory distress and cyanosis. Respiration was laboured or grunting but the rate was only moderately increased. It sometimes became Cheyne-Stokes in character before death. Physical signs in the chest other than the use of ancillary muscles and indrawing of the ribs were very uncommon. The temperature was nearly always either normal or subnormal with a cold skin and flaccid limbs.

The differential diagnosis from the acute bacterial infections was not always clear cut. Pathologically proved cases of bacterial infections on occasion presented almost as dramatically as these described and with a similar absence of chest signs. However, no such cases were ever found dead in bed. Further, interstitial mononuclear pneumonia could occasionally present in a manner quite similar to a fulminating bacterial pneumonia as for example in Cases 10 and 13.

It is thought that the condition may not always be fatal provided adequate treatment is immediately available. That this may be so is suggested by a few very similar cases which survived, examples of which are given in Appendix II.
Pathology

Externally the bodies of these children showed little or nothing abnormal. In a few instances frothy fluid was to be seen coming from the nose and possibly some cyanosis might exist, but usually there was nothing to point to a respiratory mode of death.

Internally a few petechial haemorrhages had occurred on the surfaces of the thoracic viscera and the lungs showed a slight emphysema with frequent congestion towards the bases. The lungs were usually well aerated but a patchy, dark-coloured appearance suggestive of atelectasis occurred in the area which later, on microscopic examination, proved to be affected by the pneumatic process. It was only with difficulty that any fluid could be expressed from the respiratory passages.

Microscopically, there were four principal features which were constantly present in a greater or less degree in all cases, namely, (1) emphysema, (2) thickening of the alveolar walls, (3) mononuclear cell infiltration, (4) alveolar exudate.

Perhaps the most striking feature on first examination was the emphysema, which affected all areas not directly involved in the pneumatic process. Here the alveoli were grossly distended and often ruptured. This change was most noticeable by contrast with the greatly thickened alveolar walls of the affected areas which were adjacent to them.

Thickening of the alveolar walls was perhaps the most characteristic feature of the lesion. The walls were swollen and often heavily infiltrated by large mononuclear cells and lymphocytes. There was also some congestion with red cells. The thickening was sometimes so extreme as entirely to obliterate the alveoli or these might have been diluted with fluid exudate. Adjacent areas of extreme alveolar thickening produced a solid appearance of that part of the lung. There was, however, no particular relationship to any anatomical structure such as the bronchi, where these changes were most marked. Although the inflamed tissue was scattered widely throughout the lung, it was usual for not more than half the total lung tissue to be completely involved. Exudate and emphysema, however, were spread more widely.

The exudate consisted of pale, eosinophilic staining fluid which contained islands of mononuclear cells. These were characterized by a clear homogeneous cytoplasm devoid of granules and a monocyte type of nucleus which occasionally showed a dense chromatin network and a coarse reticular pattern. These cells were of considerable size, being up to about 15 or 20 μ in diameter, and were almost round or oval. A few smaller cells were also found in the exudate. These closely resembled lymphocytes. In none of these cells could virus or other inclusion bodies be demonstrated, although careful search was made after appropriate staining by Dominich’s method, phloxine-tartrazine and Giemsa’s stains. There was also no sign of any bodies which might be interpreted as being yeasts or Plasmodia.

A similar cellular morphology was seen in the cells infiltrating the alveolar walls but here the addition of a few red cells was not unusual.

In two cases there were also numbers of polymorphs, particularly within and around the smaller bronchi. It is to be presumed that these cases had become involved in a secondary bronchopneumonia. The heart generally showed both epicardial and endocardial petechiae and right-sided dilatation. The myocardium was, however, histologically normal. Petechial haemorrhages were also present on the surface of the pleurae. The brain showed congestion and some oedema and both liver and spleen were invariably congested. The other organs showed nothing unusual.

Discussion

The cases described here are very similar both clinically and pathologically to those reported by Gruenwald and Jacobi (1951) from Brooklyn when investigating sudden death or rapidly fatal illness in infants. Davison (1945), analysing the causes of infant deaths in Birmingham, has pointed out that only a small percentage of deaths allegedly due to suffocation were due to that cause but that the majority were due to acute fulminating infection. Nevius (1953) also stressed the same point. Werne and Garrow (1947) and Carroll (1954) confirmed the work of Gruenwald and Jacobi that interstitial pneumonia was a common cause of sudden unexpected and apparently unexplained death in infants. The former stress that aspiration of vomit is not an uncommon finding in subjects dying of other causes. They consider that it should, with rare exceptions, be regarded as an agonal phenomenon. This is also confirmed by Tudor (1955). Although clinically the distinction is not always clear cut, the cases in this series like those of Gruenwald and Jacobi differ from the hyperacute bacterial pneumonias in the extreme suddenness of their onset, the prominence of collapse with low or normal temperature, and the frequent absence of auscultatory signs in the chest. There is indeed sometimes doubt in the doctor’s mind if the condition is primarily respiratory in origin. They differ clinically and pathologically from the descriptions of interstitial plasma-cell pneumonia reported by Baar
INTERSTITIAL MONONUCLEAR PNEUMONIA

(1955), Deamer and Zollinger (1953) from Switzerland, Vaněk, Jírovec and Lukeš (1953) in Czechoslovakia, Ahvenainen and Hjelt (1954) in Finland, and Lunseth, Kirmse, Prezyna and Gerth (1955), Adams (1941, 1948) and Sternberg and Rosenthal (1955) in America. These were all much more prolonged illnesses often of several weeks' duration.

Since the condition was occurring in an Asian community, the role of thiamine deficiency was considered, either as causal or aggravating. Clinically the condition was dissimilar from the accepted descriptions of infantile beri beri by Hoobler (1928), Strong (1945) and Nelson (1950). In these the onset was over some days of cardiac failure with oedema. There were attacks of colic and also of rigidity suggesting central nervous involvement. Fehily (1941) describes the acute stage of infantile beri beri as similar to a cardiac attack or bronchopneumonia with normal or subnormal temperature but with certain typical prodromata which were absent here. Such cases represented only a small proportion of the total in a community where infantile beri beri was rife. These conditions did not obtain in this series although a moderate thiamine deficiency in the breast milk is common in Gurkha mothers. Eight controls gave thiamine figures from 5-1 to 18 μg. %, averaging 9-2 μg. %. This is low in comparison with the accepted normal in the United Kingdom of 14 to 18 μg. % (Kon and Mawson, 1950). In nine rapidly fatal cases of acute respiratory disease in Gurkha infants the level averaged 5-1 μg. % (nil to 19-4) and in 10 non-fatal cases 6-7 μg. % (nil to 20-4). It was also very low in three fatal cases of interstitial pneumonia and it is therefore possible that thiamine deficiency may have played an aggravating role in the present series of cases.

It will be noted that out of 19 consecutive necropsies 11 cases showed the histological changes of interstitial mononuclear pneumonia. Eight showed the features of a bacterial pneumonia. This is not to be interpreted as the relative incidence of the two types of disease in fulminating cases. As cases had died during or as the result of long journeys to hospital, regimental medical officers were encouraged to retain such patients in the small regimental hospitals which were equipped with an enlarged pattern of the 'Queen Charlotte' oxygen box, ice cooled, and the necessary antibiotics. This undoubtedly saved the lives of many cases of fulminating bacterial infections but only a few proved cases of interstitial pneumonia were thus treated.

This arrangement also precluded effective bacterial and viral investigation.

Summary

The clinical and pathological findings in 18 cases of interstitial mononuclear pneumonia in Gurkha

and Mawson, 1950). In nine rapidly fatal cases of acute respiratory disease in Gurkha infants the level averaged 5-1 μg. % (nil to 19-4) and in 10 non-fatal cases 6-7 μg. % (nil to 20-4). It was also very low in three fatal cases of interstitial pneumonia and it is therefore possible that thiamine deficiency may have played an aggravating role in the present series of cases.

It will be noted that out of 19 consecutive necropsies 11 cases showed the histological changes of interstitial mononuclear pneumonia. Eight showed the features of a bacterial pneumonia. This is not to be interpreted as the relative incidence of the two types of disease in fulminating cases. As cases had died during or as the result of long journeys to hospital, regimental medical officers were encouraged to retain such patients in the small regimental hospitals which were equipped with an enlarged pattern of the 'Queen Charlotte' oxygen box, ice cooled, and the necessary antibiotics. This undoubtedly saved the lives of many cases of fulminating bacterial infections but only a few proved cases of interstitial pneumonia were thus treated.

This arrangement also precluded effective bacterial and viral investigation.

Summary

The clinical and pathological findings in 18 cases of interstitial mononuclear pneumonia in Gurkha

and Mawson, 1950). In nine rapidly fatal cases of acute respiratory disease in Gurkha infants the level averaged 5-1 μg. % (nil to 19-4) and in 10 non-fatal cases 6-7 μg. % (nil to 20-4). It was also very low in three fatal cases of interstitial pneumonia and it is therefore possible that thiamine deficiency may have played an aggravating role in the present series of cases.

It will be noted that out of 19 consecutive necropsies 11 cases showed the histological changes of interstitial mononuclear pneumonia. Eight showed the features of a bacterial pneumonia. This is not to be interpreted as the relative incidence of the two types of disease in fulminating cases. As cases had died during or as the result of long journeys to hospital, regimental medical officers were encouraged to retain such patients in the small regimental hospitals which were equipped with an enlarged pattern of the 'Queen Charlotte' oxygen box, ice cooled, and the necessary antibiotics. This undoubtedly saved the lives of many cases of fulminating bacterial infections but only a few proved cases of interstitial pneumonia were thus treated.

This arrangement also precluded effective bacterial and viral investigation.

Summary

The clinical and pathological findings in 18 cases of interstitial mononuclear pneumonia in Gurkha

and Mawson, 1950). In nine rapidly fatal cases of acute respiratory disease in Gurkha infants the level averaged 5-1 μg. % (nil to 19-4) and in 10 non-fatal cases 6-7 μg. % (nil to 20-4). It was also very low in three fatal cases of interstitial pneumonia and it is therefore possible that thiamine deficiency may have played an aggravating role in the present series of cases.

It will be noted that out of 19 consecutive necropsies 11 cases showed the histological changes of interstitial mononuclear pneumonia. Eight showed the features of a bacterial pneumonia. This is not to be interpreted as the relative incidence of the two types of disease in fulminating cases. As cases had died during or as the result of long journeys to hospital, regimental medical officers were encouraged to retain such patients in the small regimental hospitals which were equipped with an enlarged pattern of the 'Queen Charlotte' oxygen box, ice cooled, and the necessary antibiotics. This undoubtedly saved the lives of many cases of fulminating bacterial infections but only a few proved cases of interstitial pneumonia were thus treated.

This arrangement also precluded effective bacterial and viral investigation.

Summary

The clinical and pathological findings in 18 cases of interstitial mononuclear pneumonia in Gurkha
infants are described. Three non-fatal cases which were possibly of similar pathology are also described.

The condition is compared with certain other causes of rapid or sudden death in infants.

The aetiology is unknown. No histological evidence of viral infection was found but laboratory investigation was of necessity very incomplete. Thiamine lack was considered as a cause but on the whole evidence was against it being other than a possible aggravating factor. There was no evidence of case to case infection.

The condition is apparently a highly fatal one but there is some suggestion that prompt oxygen therapy allied with antibiotics and thiamine may be successful.

Thanks are due to Lieutenant-Colonel D. Bell, R.A.M.C., for collecting much pathological material in the early stage of this investigation and also to Dr. J. A. Simpson and Miss E. B. Cheek, of the Institute for Medical Research, Kuala Lumpur, for the estimation of milk thiamine levels.

Many regimental and hospital medical officers took an active part, and much essential administrative help was given by Colonel P. J. Richards, D.S.O., O.B.E., and Colonel J. C. Reed, C.B.E., successive Assistant Directors of Medical Services, and Lieutenant-Colonel C. W. Maisey, O.B.E., Assistant Director of Army Health at Headquarters Malaya Command.

REFERENCES


APPENDIX I

Case 1. A girl aged 6 months with previous good health. Diarrhoea and vomiting had occurred for one day, two days before she was found dead in bed.

Case 2. A boy aged 2 months who had had bronchopneumonia when aged 1 month. He had been discharged from hospital two weeks before the terminal illness. While out of hospital he had had two attacks of respiratory distress with pyrexia which had cleared rapidly. On the morning of death he had vomited twice and had had several bouts of coughing. He was not seen by a doctor until after death.

Case 3. A boy aged 6 months, whose previous health had been normal. He had a slight cough and pharyngitis in the morning and that evening developed respiratory distress, the respiration at times becoming Cheyne-Stokes in character. His pulse was weak and irregular. There were no signs in the chest. He was placed in an oxygen tent and given penicillin, but died in the early morning.

Case 4. A boy aged 2 months whose previous health was good. He had been treated for diarrhoea for two days and had recovered. On the day he was to be discharged, there was sudden onset of respiratory distress with marked stridor and cyanosis. The temperature was 98.4°F, with no signs in the chest. He was treated with oxygen and coramine, but died three hours later.

Case 5. A girl aged 6 weeks whose previous health was good. She had had mild diarrhoea for a few days which had cleared, then some vomiting, and she was admitted to hospital as a feeding problem. Her temperature was 100°F and she appeared slightly toxic. Nothing abnormal was found on examination. She was found dead in bed 10 hours after admission. No treatment had been given.

Case 6. A boy aged 1 month. He had a sudden onset of dyspnoea and crying. He was found to be cold with a pulse rate of 70 and respirations 35. There were no other abnormal physical signs. He was treated with oxygen, penicillin and coramine, but died 12 hours after admission to hospital.
Case 7. A girl aged 7 months with previous good health. There was no prodromal illness. She had a rapid onset of laboured grunting respirations and cyanosis. She vomited four times. Temperature 98·0° F., pulse 120, respirations 30. There were no abnormal physical signs other than the use of the ancillary muscles of respiration and some indrawing of the ribs. She was treated with aureomycin, penicillin and oxygen. She suddenly collapsed and died 12 hours after admission.

Case 8. A girl aged 2 months. Previous health was fair. There had been mild diarrhoea and vomiting for two weeks, but no great anxiety was felt. She was considerably better that day and evening, but she was found that night to be crying, gasping and cyanosed. Her limbs were hypotonic and there was some indrawing of the lower ribs. No other abnormal physical signs were found. She died at once before therapy could be given.

Case 9. A girl aged 7 weeks with previous good health. There was no prodromal illness. She was found in the morning to have a rapid, grunting respiration but was not markedly cyanosed. Temperature 99·2° F., pulse 130, respirations 44. There were no abnormal signs in the chest. The limbs were hypotonic. She was treated with oxygen, penicillin and chloramphenicol. She died the following morning.

Case 10. A boy aged 2 months. He was found in the morning to be pyrexial (temperature 102° F.), to be breathing rapidly and generalized rales were present in the chest. He was admitted to hospital 24 hours later and treated with oxygen, penicillin and cortisone. He died in six hours.

Case 11. A boy aged 6 weeks who had previous fair health. He had been considered to be a mild feeding problem for the previous two weeks and mother and child were admitted to hospital for instruction. The mother was wakened by a cry and found the baby unconscious, cold and cyanosed with grunting respirations. Pulse 50, respirations 44. There were no abnormal findings in the chest. The abdomen was distended. He was treated with oxygen, intravenous aureomycin, penicillin and nikethamide. No thiamine was given. He died one and a half hours later. Breast milk thiamine was 1·9 μg. %.

Case 12. A girl aged 2 months with previous good health. She had no prodromal illness and no choking incident was observed. She was found dead in bed.

Case 13. A boy aged 6 months with previous normal health. He had no prodromal illness. He was slightly off colour in the afternoon and rapidly deteriorated that evening. He was admitted to hospital in semi-coma. Temperature 102° F., pulse 140, respirations 36. There was no stridor and little cyanosis. There were generalized rales in the chest. He was treated with thiamine (50 mg. intramuscularly), penicillin, aureomycin and oxygen. His condition deteriorated further and he died 36 hours after the onset of the illness.

Case 14. A girl aged 3 months. Previous health fair. She had no prodromal illness. For two days, three weeks before the final illness, she had attacks of apnoea. During the night, before the fatal attack, she had three episodes of apnoea with rigidity and cyanosis.

On examination she appeared to have difficulty in breathing except when the head was extended. There was slight stridor when the head was flexed. Temperature 97·0° F., pulse 120, respirations 46. No other abnormal physical signs were present. No treatment was given, and 24 hours after admission to hospital the child suddenly became cyanosed, developed Cheyne-Stokes respiration and died. The mother's milk thiamine level was 4·2 μg. %.

Case 15. A boy aged 1 month with previous normal health. He had six loose stools the day before onset of the illness. He then suddenly collapsed, became unconscious, cold and cyanosed, with shallow, sighing, slow respiration. There were no abnormal signs in the chest. Temperature 96·0° F., pulse 120, respirations 18. He was treated in an oxygen tent and was given streptomycin. He showed some clinical improvement, but died on the way to hospital.

Case 16. A boy aged 6 weeks. His previous health was normal. For 24 hours he had been "unwell" and had vomited once. The bowels were open normally. There was then a rapid onset of collapse. He was cold (temperature 97·4° F.) and the respirations were rapid. There were no abnormal signs in the chest but the abdomen was very distended and hard. He was considered to be a possible case of intestinal obstruction. No treatment was given and he died 50 minutes after admission to hospital.

Case 17. A boy aged 4 months, with previous normal health. He had no prodromal illness. His mother had mild diarrhoea and vomiting and the baby was admitted to hospital with her. He was found dead in his cot.

Case 18. A boy aged 2 months with previous normal health. He was brought to the doctor because he was whimpering and crying. Nothing abnormal was found then. On the following day he was picked up by his father because he was crying, and died immediately.

APPENDIX II

Case A. A boy aged 3 months. Both mother and child were healthy. He suddenly collapsed following a breast feed, but there was no choking incident. When seen two hours later in hospital the child was conscious, but cyanosed with hypotonic limbs and a cold skin. Temperature 98·0° F. (rectal), pulse 150, respirations 54. The respirations were grunting, the ribs indrawn and the accessory muscles were being used. There were no other
abnormal physical signs. He was treated with oxygen, penicillin, chloramphenicol, elixir of phenergan and intramuscular thiamine. There was a good response in two hours which was maintained until discharge from hospital five days later. The mother’s breast milk thiamine level on the day of admission was 6·9 mg. %. After five days of 30 mg. daily, the milk thiamine level was 22·6 μg. %.

Case B. A girl aged 7 weeks. She had been in hospital for five days with gastro-enteritis, which had reacted well to sulpha therapy. On the morning she was awaiting discharge, there was a sudden onset of respiratory distress. The ribs were indrawn and the accessory muscles were being used, but there were no other abnormal signs in the chest. There was no cough. She was conscious and hydration was good, but there was slight neck rigidity and hypotonic limbs. The abdomen was distended. Temperature 99·6° F., pulse 150. She was treated in an oxygen tent and with penicillin, chloromycetin and intramuscular thiamine. By evening the respiratory rate had risen to 60, but the character was normal except that the alae nasi were working. Therapy was continued for six days and improvement was maintained. She was discharged well. The milk thiamine level was 8·4 μg. %.

Case C. A boy aged 4 months. He had a cough for one day and then an extremely rapid onset of respiratory distress. Temperature 101° F., pulse 180, respirations 30. He was conscious, well hydrated with normal skin temperature and normal muscle tone. However, he was cyanosed, the alae nasi were working and he was using the accessory muscles of respiration. There were no abnormal physical signs in the chest. He was treated in an oxygen tent with penicillin, chloramphenicol and intramuscular thiamine. He recovered rapidly and uneventfully. The milk thiamine level was 20·4 μg. %.