INFECTIOUS MONONUCLEOSIS IN BANTU CHILDREN

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Infectious mononucleosis is defined by Tidy[1,2,3] as an acute infectious disease characterized by the enlargement of lymphatic glands, changes in the blood cells, particularly mononucleosis, the presence of heterophile antibodies in the serum, and a uniformly favourable course.

The disease was first described by Pfeiffer in 1889, but it was not until 1922 that a case was reported in a Negro patient, by Longcope.[4] No further Negro cases were reported for 20 years and, although Bernstein[5] reviewed 65 cases at the Johns Hopkins Hospital in 1940, all were in White people. A year later, however, Werlin *et al.*[6] reported 4 serologically proved cases in Negro adults; since then, there have been numerous reports of Negro cases in the literature—[7,8,9,10,11,12,13,14] and most workers are now of the opinion that infectious mononucleosis is not as rare in the Negro as had hitherto been believed. Despite this, relatively few cases have been shown to occur in Negro infants and children.

The first reported cases of the disease in Negro children were those of Johnson[7] in 1944. One year later Blain and Von der Heide[9] described a further case in a boy of 6 years. In 1949 Bower *et al.*[19] described a case. Chernoff and Josephson,[15] in 1951, reported a case associated with acute erythroblastopenia, and Harley,[16] reviewing 15 cases, found 9 in Negro children, the youngest of whom was 9 months. In the same year Walker[17] described a case in an infant of 9 weeks. Finally, in 1952, Karpinski[18] was the first to describe a case of infectious mononucleosis in a Negro child who developed neurological manifestations. A review of the available literature thus reveals only 16 cases of infectious mononucleosis in Negro infants and children. We were unable to find any proven cases reported in Bantu children in Southern Africa.

We have reviewed the admissions to the Paediatric Department of Coronation Hospital, Johannesburg, over the past 6 years and have been unable to trace any proven cases of infectious mononucleosis during the 4 years 1950-1953; while in the 2½ years commencing 1954 we have been able to confirm 4 cases, which we present here.

CASE REPORTS

Case 1

J.D N., 1-year-old male Bantu child, was admitted to the Paediatric Ward on 22 September 1955 with a history of cough for 2 days, pyrexia for 1 day, and restlessness. Three weeks previously the child had spent 4 days in hospital with gastro-enteritis and dehydration, requiring intravenous therapy.

The child was obviously ill, coughing and dyspnoeic. The temperature was 105° F, pulse 160 per minute, and respirations 50 per minute. The throat was slightly injected. Submandibular, tonsillar and cervical lymph-nodes were palpable, but not tender. Signs of consolidation were present at the left base and right apex. The cardio-vascular and central nervous systems were normal. Liver and spleen were not palpable. There was no cyanosis, oedema or pigmentation of the extremities. A diagnosis of pneumonia was made and treatment instituted, viz., penicillin, 250,000 units 6-hourly, and streptomycin, ½ g. twice daily.

Progress and Investigations. On the 2nd hospital day, the temperature had fallen to 100° F. Full blood-count showed haemoglobin 7·2 g.% and leucocytes 15,600 per c.mm. (neutrophils 43%, monocytes 3%, lymphocytes 54%). There was a marked hypochromic anaemia. X-ray examination of the chest showed patchy consolidation involving the lingular segment of the left upper lobe, the left base, and the right apex. Hilar adenopathy was present.

On the 3rd hospital day, the temperature rose to 103° F with no change in the physical signs but, by the 5th day, the temperature had fallen to normal and remained so for the rest of the stay in hospital. The modified Ide, patch and Mantoux tests were negative. The liver and spleen were now palpable. Two days later the heterophile antibody titre was 1/112 and the differential absorption tests were positive for glandular fever.

A blood transfusion of 275 c.c. was given on the 9th day. On

the 12th hospital day the haemoglobin was 13·5 g.% and leucocytes 15,700 per c.mm. (neutrophils 40%, monocytes 3%, lymphocytes 57%). Atypical lymphocytes were present. Liver function tests were as follows: Thymol turbidity 4 units, thymol flocculation ++++, colloidal red ++, Takata Ara reaction negative, zinc-sulphate turbidity 17·8 units, alkaline phosphatase 9·4 King-Armstrong units, total serum-bilirubin 1·0 mg.%, and serum-proteins 7·2 g.% (albumin 4·0, globulin 3·2.)

On the 15th hospital day the spleen was no longer palpable, but the liver was still enlarged and the neck glands were still present. X-ray examination of the chest showed clearing of the right apex and partial clearing of the left base. By the 20th day the blood count had returned to normal, and the heterophile antibody titre had now risen to 1/224 with positive absorption tests for glandular fever. On the 33rd day small palpable neck glands were still present, but the liver was no longer palpable. Clinically, and on X-ray examination, the chest was clear and the patient was discharged.

Case 2

J.R., 10-month-old male Bantu infant, was admitted to hospital on 31 August 1955 with a history of a bulging fontanelle for 4 days. There had been no pyrexia, vomiting or diarrhoea.

The infant was in apparent good health. The temperature was 98° F, pulse rate 130 per minute, and respirations 28 per minute. Signs of rickets were present, viz. cranio-tabes, rickety rosary and enlarged wrist-joint epiphyses. Ears, nose and throat were normal. The anterior fontanelle was large, firm and bulging. There was no neck stiffness and Kernig's sign was negative. Respiratory and cardio-vascular systems were normal. The cranial nerves were intact. Fundi were normal. The motor system showed no abnormality and muscle tone was normal. There was no interference with sensation. Reflexes were normal and equal. The liver and spleen were both palpable 2 fingers below the costal margins. The rest of the examination was normal.

Progress and Investigations. Lumbar puncture showed the cerebrospinal fluid to be under pressure of 300 mm. of water, and the fluid was found to contain 1 lymphocyte per c.mm. and protein 16 mg.%. On the 2nd hospital day, full blood-count showed haemoglobin 10·5 g.% and leucocytes 10,000 per c.mm. (neutrophils 31%, monocytes 4%, lymphocytes 62%, eosinophils 1%, basophils 1%). Some atypical lymphocytes were seen. The heterophile antibody titre was positive 1/112, confirmed by differential absorption tests. Viral and ricketsial complement-fixation tests were negative. The typhoid, paratyphoid, brucella and proteus agglutination tests were negative. X-ray examination of the chest and skull was normal. By the 4th hospital day, the fontanelle was normal.

On the 7th hospital day, haemoglobin was 10·7 g.% and leucocytes 8,300 per c.mm. (neutrophils 34%, monocytes 10%, lymphocytes 51%, atypical lymphocytes 5%). The heterophile antibody titre was 1/56. Lymph glands were now palpable in the axillae and neck. On the 10th day, a Mantoux test was negative. Liver function tests were as follows: Thymol turbidity 3 units, thymol flocculation negative, colloidal red ++, Takata-Ara reaction negative, zinc-sulphate turbidity 12·4 units, alkaline phosphatase 69·6 King-Armstrong units, total serum-bilirubin 0·5 mgm.%, and serum-proteins 6·1 gm.% (albumin 3·3, globulin 2·8).

On the 14th hospital day, the spleen, liver and axillary, neck and inguinal glands were just palpable. The patient was discharged the following day.

Case 3

T.K., a 2-month-old Bantu male child, was admitted on 31 January 1956 with a history of diarrhoea and vomiting for 2 weeks. The child was grossly dehydrated and acidotic. The temperature was 100° F, pulse rate 124 per minute, and respiration 30 per minute. A few small glands were palpable on both sides of the neck. The respiratory, cardio-vascular and central nervous systems were normal. The liver and spleen were not palpable. Intravenous fluid therapy was instituted, the child rehydrated and the acidosis corrected.

By the 3rd hospital day, the temperature had fallen to normal, where it remained for the rest of the patient's stay in hospital. On the 4th day, a full blood-count showed the haemoglobin to be 11·5 g.% and leucocytes 10,200 per c.mm. The heterophile antibody titre was positive 1/112, and was confirmed by differential absorption tests.

On the 11th day, leucocytes were 10,000 per c.mm. (neutrophils 53%, monocytes 3%, lymphocytes 44%). The heterophile antibody titre was now 1/224, and was confirmed by the differential absorption tests. Liver function tests were as follows:thymol turbidity 10 units, thymol flocculation ++++, Takata-Ara reaction negative, zinc-sulphate turbidity 11·4 units, colloidal red ++++, alkaline phosphatase 23·8 King-Armstrong units, total serum-bilirubin 0·5 mg.% and serum-protein 7·0 g.% (albumin 3·1, globulin 3·9). By the 23rd hospital day, the lymph glands in the neck were no longer palpable and 2 days later, the child was discharged clinically well.

Case 4

D.B., a 5-year-old Bantu female child, was admitted to hospital on 1 July 1954 with a history of progressive swelling of the abdomen for 4 months. Temperature 99·2° F, pulse rate 130 per minute and respiration 26 per minute. Axillary, inguinal and epitrochlear glands palpable but not tender. The abdomen was distended, and the liver and spleen were palpable 4 and 6 fingers, respectively, below the costal margin. The cardio-vascular, respiratory and central nervous systems were normal.

Progress and Investigations. On the 2nd hospital day, the haemoglobin was 10·6 g.%, and leucocytes 7,800 per c.mm. (neutrophils 51%, monocytes 1%, lymphocytes 43%, eosinophils 3%, basophils 2%). Malarial parasites were not observed, and the bilharzial complement-fixation test was negative. Examination of the urine and stools revealed nothing abnormal. Liver function tests were as follows: thymol turbidity 9·0 units, thymol flocculation ++++, colloidal red +++, Takata-Ara ++++, zinc turbidity 47·4 units, alkaline phosphatase 17·5 King-Armstrong units, total serum-bilirubin 0·4 mg.%, and serum-protein 8·2 g.% (albumin 3·2, globulin 5·0).

On the 20th hospital day, the spleen was smaller, but the left inguinal glands had increased in size. On the 23rd day, the heterophile antibody test was positive 1/112, and was confirmed by the differential absorption tests. On the 31st day, the heterophile antibody titre was again positive 1/112 and confirmed by the differential absorption tests. On the 42nd day, leucocytes were 15,800 per c.mm. (neutrophils 34%, monocytes 4%, lymphocytes 49%, atypical lymphocytes 13%).

The patient was discharged on the 49th hospital day. At that stage the liver and spleen were still palpable and the axillary, inguinal and epitrochlear glands were still enlarged.

DISCUSSION

Infectious mononucleosis, although recognized as a disease entity for over 60 years, has up to the present been reported in relatively few Negro infants and children. The occurrence of the disease does not appear to be limited by factors of geography or race; indeed, it is world-wide in distribution.[1,25] There is no known reason why the disease should not affect Negro infants and children just as commonly as Whites, and it may probably be that many cases are not diagnosed because the disease has an exceptionally low mortality and only a moderate morbidity.

Although the diagnosis of infectious mononucleosis may easily be overlooked because of its relatively benign course in the large majority of cases, it has become increasingly apparent that this disease is not necessarily always such a benign and self-limited one. On the contrary, evidence has accumulated in the past few years to indicate that the disease process is a systemic one, its clinical manifestations being dependent upon the system or systems involved. Instances of hepatitis,[5,20,21,22,23] myocarditis,[5,14] pneumonitis,[5] encephalitis,[5,18] and interstitial nephritis,[5] resulting from infectious mononucleosis have been reasonably well documented. In an excellent review of the literature

in 1952 Karpinski[18] points out that changes in the central nervous system in children caused by infectious mononucleosis are far more common than one is generally aware of, and that this disease should always be considered in the differential diagnosis of the numerous 'idiopathic' encephalitides and meningitides seen in paediatric practice.

Diagnostic Criteria

The criteria for diagnosing infectious mononucleosis in our 4 cases presented above were based upon the following five points:

1. *Lymphadenopathy.* Enlargement of one or other group of lymph nodes, or generalized glandular enlargement, is usually a constant finding in cases of infectious mononucleosis.[5,26] In a minority of cases, however, glandular enlargement may be absent in spite of a positive serological test.[27]

2. *Hepatomegaly and Splenomegaly.* Splenomegaly is a common feature in infectious mononucleosis and, according to Bernstein,[5] occurs in 50% of cases. Hepatomegaly, however, occurs less frequently (24%) despite the fact that hepatitis is frequently present.

3. *Mononucleosis and Atypical Lymphocytes.* There is no blood picture that is exclusively typical of infectious mononucleosis;[3,5] however, a mononucleosis appears at some stage of the disease[5] and, associated with this, is the appearance of atypical mononuclear cells which, although not diagnostic of the disease, is highly suggestive.[3]

4. *Positive Heterophile Antibody Reaction.* In 1932 Paul and Bunnell[28] discovered antibodies that could react with certain antigens which were different from, and phylogenetically unrelated to, those instrumental in producing the antibody response. These heterophile antibodies, as they are called, are present in low titre in normal serum but have been shown to occur in high titre in the serum of patients suffering from infectious mononucleosis.[3,28,29] The differential absorption test is a confirmatory test for infectious mononucleosis, the agglutinins in the serum of cases of that disease[30,31] being absorbed by boiled beef cells and not by guinea-pig kidney. A titre of 1/56, when accompanied by positive absorption-tests, is regarded as being absolute diagnostic evidence of infectious mononucleosis.[3,30,31]

5. *Abnormal Liver Function Tests.* Hepatitis, not necessarily accompanied by jaundice or hepatomegaly, has been shown to occur in infectious mononucleosis by many workers.[20,21,22,32,33] Brown *et al.*[23] and Gall[33] have suggested that all cases of infectious mononucleosis will show some degree of liver damage, and that hepatic involvement is a usual, rather than an incidental, occurrence. Leibowitz and Brody[20] question the validity of the diagnosis in the absence of liver damage.

Review of Presenting Signs and Symptoms

After a study of the 16 cases so far reported in Negro infants and children, and our own 4 Bantu cases, we feel that it may be of some interest to review briefly and analyse the modes of presentation and the physical findings with which the cases presented.

Of our 4 cases, 1 presented with respiratory distress and pneumonia, 1 as an acute diarrhoea and vomiting and dehydration, 1 with a bulging fontanelle, and 1 with generalized lymphadenopathy and hepatosplenomegaly for investigation. All 4 cases showed lymphadenopathy on admission to hospital or developed palpable lymph-nodes within the first week of their illness. Hepatomegaly and splenomegaly were present in 3 of our cases, and atypical mononuclear cells were found to be present in the same 3 cases. In every case the heterophile antibody reaction showed diagnostic titres of 1/112 or higher with positive differential absorption tests. Abnormal liver function tests were present in all 4 cases, indicating the presence of hepatic damage despite the absence of jaundice. The age incidence ranged from 2 months to 5 years.

Of the 9 cases reported by Harley,[16] 6 presented with membranous tonsillitis and were admitted to hospital in order to exclude diphtheria. Of the other 3 cases, all had generalized lymphadenopathy as the major presenting symptom and were investigated to rule out tuberculosis or leukaemia; one of them had a maculo-papular rash resembling measles. The age incidence of these 9 cases ranged from 9 months to 7 years.

Of the remaining 7 reported cases, most of the children were severely ill on admission, many of them having temperatures between 101°F and 105°F. The youngest of the 7 was 9 weeks old and presented with acute diarrhoea and vomiting.[17] The other 6 cases ranged in age from 5 months to 10 years. Five of them presented with acute membranous tonsillitis (making a total of 11 cases with this symptom) and were severely ill children. Two presented with signs of involvement of the central nervous system—1 with headache and fever and 1 with drowsiness and irritability. The latter was found to have 297 mononuclear cells per c.mm. in the cerebrospinal fluid, recovery taking place after 1 week.[18] One child presented with respiratory distress.[19] Four of these 7 children had enlarged palpable spleens with generalized lymphadenopathy, and 2 had enlarged livers.

CONCLUSION

From the foregoing it will be seen that by far the commonest presenting symptom in the 16 reviewed cases reported by other authors was an acute membranous tonsillitis, in most cases accompanied by a generalized lymphadenopathy and splenomegaly. None of our cases presented thus, their clinical picture being somewhat atypical and differing from the generally accepted modes of presentation as described by Tidy.[1, 2, 3] It would appear, therefore, that infectious mononucleosis may present in a variety of ways and is protean in its manifestations. It is for this reason that cases of this disease may be easily overlooked. Although there were no deaths in these cases, it should be noted that many of the children went through a stage of high fever and were severely ill. Central-nervous-system signs were present in 10% of the total cases reported so far, acute diarrhoea and vomiting in 10%, and respiratory distress in 10%. Splenomegaly was present in 35% of cases and hepatomegaly in 25%.

We are of the opinion that mild cases of infectious mononucleosis are not uncommon among Bantu infants and children, and that, were this condition looked for a little more carefully, the incidence would probably equal that in any other race. Although the disease is benign in the majority of cases, it is important to bear in mind that the more severe manifestations of the disease are by no means rare.

SUMMARY

1. A review of the literature on the incidence of infectious mononucleosis in the Negro, with particular reference to its occurrence in Negro infants and children, is presented.

2. Four cases of infectious mononucleosis in Bantu infants and children at Coronation Hospital, Johannesburg, are described.

3. The presenting symptoms and signs in the 20 reported cases of infectious mononucleosis in Negro infants and children are briefly reviewed and analysed.

4. It is our opinion that infectious mononucleosis in Bantu infants and children is not as uncommon as has hitherto been believed.

5. The disease may present in a variety of ways and is protean in its manifestations.

6. Although the disease is benign in the majority of cases, more severe manifestations are by no means rare.

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REFERENCES

1. Tidy, H. L. (1949): *Synopsis of Medicine*, 9th ed., p. 328. Bristol: John Wright and Sons Ltd.
2. *Idem* (1934): Lancet, **2,** 180 and 236.
3. *Idem* (1950): Postgrad. Med. J., **26,** 9.
4. Longcope, W. T. (1922): Amer. J. Med. Sci., **164,** 781.
5. Bernstein, A. (1940): Medicine, **19,** 85.
6. Werlin, S. J., Dolgopol, V. B. and Stern, M. E. (1941): Amer. J. Med. Sci., **201,** 474.
7. Johnson, R. D. (1944): J. Amer. Med. Assoc., **124,** 1254.
8. Ray, E. S. and Cecil, R. C. (1944): Southern Med. J. **37,** 543.
9. Blain, A. and Von der Heide, E. C. (1945): Amer. J. Med. Sci., **209,** 587.
10. Steward, D. N. (1947): U.S. Nav. M. Bull., **47,** 889.
11. Gardner, H. T. and Paul, J. R. (1947): Yale J. Biol. Med., **19,** 839.
12. Creaturo, N. E. Akerson, I. B. and Flanagan, M. M. (1948): Connecticut St. Med. J., **12,** 526.
13. Wilson, S. J., Ward, C. E. and Gray, L. W. (1949): Blood, **4,** 189.
14. Miller, H., Uriccho, J. F. and Phillips, R. W. (1953): New Engl. J. Med., **249,** 136.
15. Chernoff, A. I. and Josephson, A. M. (1951): Amer. J. Dis. Child., **82,** 310.
16. Harley, J. F. (1951): J. Pediat., **39,** 303.
17. Walker, S. H. (1951): U.S. Armed Forces Med. J. **2,** 1875.
18. Karpinski, F. E. (1952): Pediatrics, **10,** 265.
19. Bower, A. G., Affeldt, J. E. and West, H. (1949): J. Pediat., **35,** 58.
20. Leibowitz, S. and Brody, H. (1950): Amer. J. Med., **8,** 675.
21. Cohn, C. and Lidman, B. I. (1946): J. Clin. Invest., **25,** 145.
22. Evans, A. S. (1948): *Ibid.*, **27,** 106.
23. Brown, J. W., Sims, J. L., White, E. and Clifford, J. E. (1949): Amer. J. Med., **6,** 321.
24. Wechsler, H. F., Rosenblum, A. H. and Sills, C. T. (1946): Ann. Intern. Med., **25,** 113.
25. Rathmell, T. K., Greeley, J. P. and Granger, J. R. (1950): Amer. J. Clin. Path., **20,** 977.
26. Editorial (1947): J. Amer. Med. Assoc., **134,** 1548.
27. Van der Meer, R., Lutterloh, C. H. and Pilot, J. (1945): Amer. J. Med. Sci., **210,** 765.
28. Paul, J. R. and Bunnell, W. W. (1953): *Ibid.*, **183,** 90.
29. Bunnell, W. W. (1933): *Ibid.*, **186,** 346.
30. Leibowitz, S. (1952): Amer. J. Med., **13,** 172.
31. Kaufman, R. E. (1944): Ann. Intern. Med., **21,** 230.
32. Petersen, R. E. (1948): J. Lab. Clin. Med., **33,** 1258.
33. Gall, E. A. (1947): Amer. J. Clin. Path., **17,** 529.