A Clinical Study of

Infectious Mononucleosis and Toxoplasmosis

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John Wright & Sons Limited · Bristol

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BRISTOL
JOHN WRIGHT
1973

ISBN 0 7236 0326 X

Printed in Great Britain by John Wright and Sons Ltd. at The Stonebridge Press, Bristol BS4 5NU

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Acknowledgements

We are indebted to Dr. Donald Chalmers and Professor Hermann Lehmann, of the John Bonnett Laboratories of Cambridge University, and their staff for the haematological and biochemical investigations. We should also like to thank Dr. Granville Naylor and the staff of the Public Health Laboratory Service for carrying out the Paul-Bunnell tests and bacteriological investigations.

The photographs and illustrations were prepared by the Medical Photographic Department of the United Cambridge Hospitals under the direction of Mr. L. Beard.

Contents

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Chapter 1 **Introduction**

IN 1889 a German physician called Emil Pfeiffer read a paper in Cologne on a disease which he called *Drüsenfieber*. This was translated into English as 'glandular fever' and is now more often known as 'infectious mononucleosis'.

The condition which Pfeiffer described took two forms, but both affected children mainly in the 5–8 years age-group. The commonest form was of sudden onset with high fever, pain in the extremities, restlessness, and perhaps vomiting. The throat was very reddened. There was no exudate or membrane but there were numerous swollen painful lymph-glands around the entire neck, especially around the sternomastoid and nape of the neck. The child was better by the following day with a normal temperature, and the lymphatic glandular enlargement disappeared completely within a few days. The other form which he called the 'chronic' form lasted 8–10 days with a fever persisting for several days and enlargement of the liver and spleen. Pfeiffer said that the throat becomes reddened but there is never any membrane, nor had he ever seen enlargement of the axillary or inguinal glands, or a rash. He drew attention to the fact that although the lymph-glands in front of the sternomastoid may enlarge there is nothing characteristic about them as they frequently enlarge in other diseases such as sore throat and stomatitis; but when the glands at the back of the sternomastoid and nape of the neck enlarge rapidly and become painful, and then return to normal in a few days or weeks, then one is dealing with the disease he called *Drüsenfieber*. He said that the glands never suppurate and although a child may remain pale and anaemic for some time the prognosis is always favourable. The condition is considered infectious as it occurred in epidemics and house epidemics.

Following Pfeiffer's account of this disease, various other reports appeared in the literature. The first paper in English was by a physician called Williams in 1897 who described the illness of a 5-year-old girl with cervical adenopathy, granular pharyngitis, abdominal pain, hepatomegaly but no splenomegaly, whose elder and younger brothers had similar but milder illnesses.

Rudolf (1914) described an epidemic of cervical adenitis in children, but as one child had suppurating neck glands which required incision, and from which a haemolytic streptococcus was grown, this may well not have been infectious mononucleosis. In the same year Stark (1914) described an epidemic of 30 cases, all children under 12 years old.

In 1921 Tidy and Morley published the first full account in the British literature of the disease then called 'glandular fever'. They defined the condition as 'an acute infectious disease principally of children characterised by rapid enlargement of the cervical glands and by less constant enlargement of the liver and spleen, axillary, inguinal and other glands'. They, like Pfeiffer, drew attention to the fact that the cervical glands characteristically affected are those deep to the sternomastoid muscle about the middle of its length. They also pointed out that the swelling was different in position and general condition from glandular swellings associated with infections of the tonsils, teeth, and nasopharynx. They found that usually there was no clinical abnormality of the fauces, or only occasionally a little reddening of the pharynx which bore no relationship to the size of the cervical glands. About 80 per cent of their patients were under the age of 12 years, and the commonest complication was haemorrhagic nephritis. This raises the question of whether or not cases of acute haemolytic streptococcal throat infections were being misdiagnosed as glandular fever. However, as stress is laid in the description of the disease on the absence of changes in the throat, and the characteristic enlargement of the posterior cervical glands, this seems unlikely.

The specific haematological diagnostic test for infectious mononucleosis was described by Paul and Bunnell in 1932 and is discussed in more detail in Chapter 6, HAEMATOLOGY.

Since those early descriptions of the disease, the clinical and epidemiological picture has changed considerably. Infectious mononucleosis still, in many respects, remains a challenge. The causative agent, presumed to be a virus, has not yet been identified.

Recent work by Niederman, McCollum, Henle, and Henle (1968) suggests that the Epstein-Barr virus may be implicated in the aetiology. The findings are discussed in Chapter 2.

The disease presents in many different ways, the complications are varied, and the severity and length of illness unpredictable. Because of the protean nature of the disease we have taken a great interest in it for some considerable time. In writing this monograph we have attempted to stress the diagnostic features of clinical significance, and give an account of the various aspects of the disease as regards its epidemiology, clinical and laboratory findings, and treatment with special regard to the features we have noted in a close study of 270 patients with confirmed infectious mononucleosis admitted to Brookfields Hospital, Cambridge, over a 10-year period.

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THE age incidence of infectious mononucleosis has altered considerably since it was first described, and it is now primarily a disease of young adults rather than children, and no longer occurs in epidemics. We have never seen a child under 5 years suffering from the disease although Phillips and Stone (1956) have reported the disease in a child aged 6 weeks. In our series 75 per cent of patients are in the age-group of 18–23 years. Less than 5 per cent of patients with confirmed infectious mononucleosis are nowadays under the age of 15 years, about 8 per cent are between 15 and 18 years old, and about 12 per cent aged 24 and over. The high percentage of cases in the age-group 18–23 years is to a certain extent explained by the large number of undergraduates in Cambridge. The disease is uncommon over the age of 30 years and our oldest patient was 47 years.

Although infectious mononucleosis may be suspected frequently on clinical grounds many patients, especially children, will be found on further investigation to be suffering from other diseases. Penman (1966) saw all patients who were suspected of having infectious mononucleosis in three communities near Portsmouth over a 12-month period. Out of 55 patients he found 38 not to be suffering from infectious mononucleosis, and of those 38, 23 were under 15 years of age, thus supporting the view that the disease is now not common in children although frequently erroneously diagnosed on clinical grounds by general practitioners.

The degree of infectivity at the present time is very low. We traced the close contacts of 30 patients over a 15-month period and obtained blood samples from them. No contact, even where there had been frequent kissing during the early stages of the disease, developed any clinical or haematological evidence of the disease over a 3-month period. On the other hand, of the 270 patients in the whole series investigated from the point of view of their possible source of infection, 2 had had close contact with confirmed cases 3 months previously, one 8 weeks previously, and one 6 weeks previously, suggesting an incubation period of 6–12 weeks.

Further confirmation of this was found when we analysed the peak incidence of admissions for infectious mononucleosis

throughout the year. Cambridge being a university town has a large floating population of undergraduates. We found that the greatest number of patients with infectious mononucleosis was admitted in May, with a slightly smaller number in February. However, when we related the number of patients admitted with infectious mononucleosis to the total number of admissions for all infectious diseases for each month, we found that in February, May, and November infectious mononucleosis accounted for 14 per cent of all admissions (*Fig.* 1). These months correspond

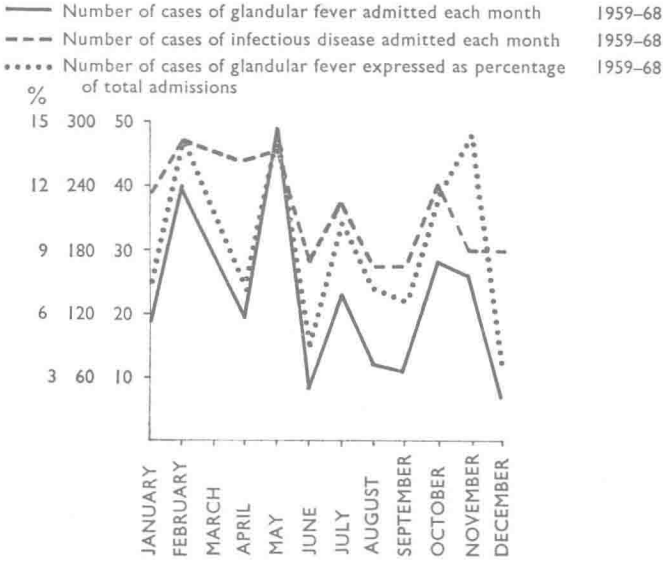

Fig. 1. Seasonal distribution.

with a return of the undergraduate population from vacation 4–6 weeks previously and suggest a similar incubation period of 6–10 weeks.

In 1968 Henle, Henle, and Diehl published their findings on a herpes-type virus which was detected in cell lines derived from Burkitt's lymphoma and which they called 'EB virus' (EBV). They found from serum surveys that this agent has a world-wide distribution and that among American children antibodies to this virus showed a similar pattern to that of antibodies to other common viruses such as measles and mumps, and persisted in the blood for a very long time. They also found a much higher

incidence of antibodies in children aged 4–15 years from the lower socio-economic levels than in those from well-to-do families.

In the same paper they report their investigations in the case of a laboratory worker who before developing infectious mononucleosis had no EBV antibodies in her serum but had EBV antibodies in her blood a week later. This chance finding led to further studies on the relationship of EBV to infectious mononucleosis. Niederman, McCollum, Henle, and Henle (1968) found that each of 29 patients who contracted infectious mononucleosis developed antibodies against EBV. These antibodies were not present before the onset of infectious mononucleosis, appeared early in the course of the disease, and persisted for years, probably for life. They are distinct from the heterophile antibodies found by the Paul-Bunnell test, which usually disappear within a few months. Their findings strongly suggest that EBV or a very closely related virus is responsible for infectious mononucleosis. Further work of course remains to be done in this field, but surveys of EBV antibodies among varying groups of population should help considerably in establishing the true incidence of infectious mononucleosis in the community, the incidence of sub-clinical infections, and probable mode of spread.

The change in the maximum age incidence of the disease over the past 50 years to the adolescent and early adult group rather than to children under 12 years may be in part at least due to changing socio-economic patterns. Henle and others (1968) found a much higher incidence of EBV antibodies in children of 4–15 years who came from poor homes than in those from more affluent families. If a similar virus is responsible for causing infectious mononucleosis one would expect a higher incidence of the disease among the children of the better-off section of the population in the late teens and early twenties as compared with children of manual workers of the same age-group. With most other virus infections, e.g., mumps and chicken-pox, young children on the whole tend to have a milder illness than those who are infected in their adolescence and adult life, and there are no doubt many very mild or subclinical cases which are missed in early childhood. This may explain the relatively high incidence of overt infectious mononucleosis among such populations as college students and nurses as compared with manual workers in Britain and America and also at least partly explain its low incidence among Negroes

(Hoagland, 1967) and its absence among Asians in Malaya (Tan, 1967).

A comparison may be drawn with the virus of poliomyelitis which in the primitive communities of the tropics rarely occurs as clinically recognizable disease whereas in Western Europe and America, before the introduction of an efficient vaccine, frequent epidemics with many cases of severe paralysis and deaths occurred. The disease was usually most severe in the older victims and Olin (1952) found that the death-rate of patients over 25 years of age was two to five times greater than for children under 7 years. The virus of poliomyelitis is known to have a world-wide distribution. The rarity of clinical disease in low socio-economic groups is presumably due to active infection of children at a very early age while they are still protected by maternal antibodies and thus able to build up an active immunity of their own before their passive immunity has waned completely.

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THE mode of onset of infectious mononucleosis is in the majority of cases insidious, the prodromal symptoms extending over a period of 4–7 days and in some cases even longer.

Sometimes, on the other hand, especially in those presenting with neurological manifestations, the onset may be very acute indeed. This is well illustrated in the case of a female undergraduate found unconscious in her room early one afternoon. We interviewed her tutor and fellow undergraduates in whose company she had been the previous evening, and they all said she had appeared perfectly well then. The following morning she apparently complained of a headache and a feeling of general malaise, and stayed in bed. By lunch time that day she was drowsy and lethargic and shortly afterwards was found to be unconscious.

On admission to hospital she was found to be deeply unconscious, responding only to painful stimuli. She was very meningeal, but there were no localizing neurological signs. There were none of the changes one finds so often in infectious mononucleosis in the mouth or throat, nor was there any lymphatic gland or splenic enlargement. Her cardiovascular and respiratory systems were normal.

A lumbar puncture gave a clear cerebrospinal fluid containing 130 lymphocytes per mm.^{3} The protein and glucose contents were normal. Her Paul-Bunnell test was positive at a titre of 1 : 2560.

A few days afterwards she did develop the type of lymphadenopathy one associates with infectious mononucleosis. At no time, however, did she develop any changes in the oral cavity such as the petechiae and small punctate haemorrhages found on the buccal mucous surfaces and on the palate, nor was there ever any tonsillar exudate. After 48 hours in hospital she began to show signs of improvement, eventually making a complete recovery without any specific form of treatment.

Here we have a case with an extremely short prodromal history presenting in much the same way as a fulminating bacterial meningitis. This, in our experience, is extremely rare. Two other interesting features are the high Paul-Bunnell titre (1 : 2560) within 24 hours of the onset of symptoms, and the development of lymphadenopathy after the onset of the acute illness. This sequence of events is analogous to what may happen in some other viral infections

such as mumps where neurological involvement may precede the swelling of the salivary glands or where occasionally encephalitis may be the only manifestation of the disease. A case with severe neurological complications of infectious mononucleosis is described in the Appendix (*Case* 1).

We found that malaise was the symptom most often complained of initially, but this is too non-specific and common a complaint to be of any value in diagnosis. Eighty-eight per cent of patients in our series complained of sore throat. For those physicians still interested in basing their diagnoses on a thorough clinical examination of the patient, the oral cavity is a most rewarding hunting ground. Changes occur in the tonsils, pharynx, palate, and buccal mucosa which are fully described in Chapter 4, CLINICAL FINDINGS. They must be looked for carefully with a spatula and a really efficient torch. Such an inspection is indeed a very important part of the examination of any patient presenting with a fever of uncertain origin. In quite a number of patients with infectious mononucleosis the sore throat is very painful indeed and associated with considerable dysphagia and pooling of saliva.

About 64 per cent of patients noticed enlargement of their lymphatic glands usually in the posterior cervical and occipital regions. Those glands were never tender, but some patients who had superadded bacterial throat infections did have large tender glands under the upper borders of their sternomastoid muscles which were extremely painful to touch.

Sixty-two per cent of patients complained of headache—usually frontal and behind the eyes. This again is a non-specific symptom common to many fevers and of no value in diagnosis. Six per cent of our series, however, did have a meningo-encephalitis. In these cases the headache was generally much more severe and typically occipital in location.

Rigors, feverishness, and sweating are all common symptoms. The attacks of sweating are fairly characteristic, occurring usually in the late evening and during the night and literally soaking the patient—the sort of drenching sweats one used to associate with cases of galloping phthisis.

Twenty-seven per cent of patients complaining of anorexia and vomiting may seem rather a high proportion, but when one considers that the serum transaminase levels are increased in over 80 per cent of patients it is perhaps surprising that this number is not larger.

In an illness which is characterized by a period of continued fever it is perhaps surprising that only 21 per cent complained of muscle pains. Abdominal pain was a symptom only in 8 per cent of patients, but such a complaint should always alert one to the possibility of a ruptured spleen, as should a complaint of dizziness and faintness.

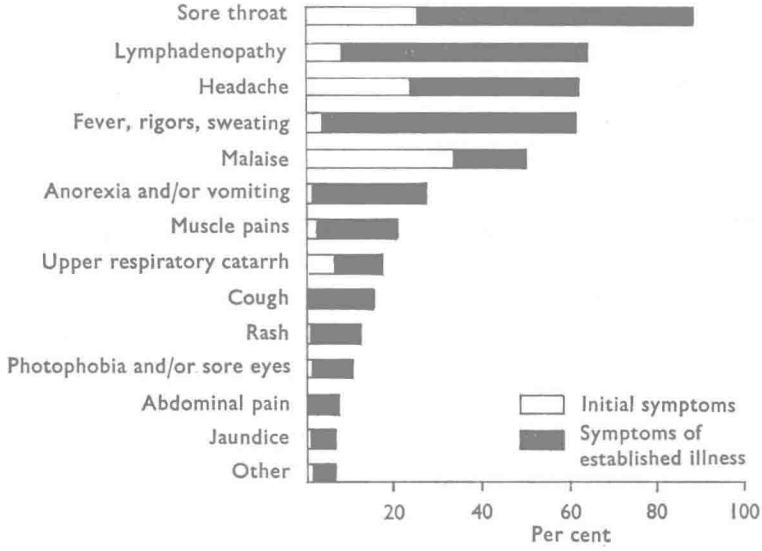

Fig. 2. Symptoms.

Other symptoms were infrequent. Five patients had an epistaxis, again a surprisingly low figure in view of the common occurrence of punctate haemorrhages on the buccal mucosa and possibly on other mucosal surfaces, and the not uncommon finding of reduced blood platelet levels. One patient had a haemoptysis and 1 a haematemesis, neither of which was severe, and for which no other underlying pathology was demonstrated. Two patients complained of diarrhoea, but 1 was found to be suffering from a concurrent attack of Sonne dysentery.

The various symptoms and their frequency are illustrated in graphic form in *Fig.* 2.