STEROID THERAPY IN GLANDULAR FEVER

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Glandular fever or infectious mononucleosis is a disease of undetermined aetiology which may present variously. The literature is replete with accounts of its complications. In spite of the usually benign course, there remains a small mortality rate and it is therefore not surprising that adrenal corticosteroid treatment has been used in the severest forms of the illness. Doran *et al.*³ described the use of ACTH in the anginose type of glandular fever, and Mandel⁶ reported a case of impending respiratory obstruction due to anginose glandular fever in which ACTH avoided the need for tracheotomy. A patient with Guillain-Barré syndrome in association with glandular fever was treated successfully with cortisone,⁴ and another with thrombocytopenia also responded to cortisone,⁵ though it should be mentioned that a platelet agglutinating factor was present in this patient. Finally the use of prednisone in the successful treatment of a severe anginose case has been described by Creditor *et al.*,² and several patients were treated by Mason *et al.*⁷ for very short periods and with indeterminate results.

The above and other reports suggest that steroids are effective in the treatment of this condition, and it is the purpose of this paper to consider the possible indications for such therapy, supported by short case histories in 10 patients.

The diagnosis of glandular fever in our cases was made clinically, and by the presence of a Paul-Bunnell test positive in diagnostic titre after absorption by guinea-pig kidney,¹ and/or the presence of atypical lymphocytes in the peripheral blood.

CASE HISTORIES

Case 1

T.C., Male, aet. 19. Admitted 31.7.59

Six months before admission this patient had a transient purpuric rash which required no treatment. Haemoglobin 100%, white cell count 7,600/mm.³, lymphocytes 24%. Platelets 46,000/mm.³ Bleeding time (Dukes) 12 minutes. He was subsequently well until

three days before admission when purpura appeared. On examination he was afebrile with purpura and ecchymoses on palate, face, arms and legs. Two small lymph glands were felt in the neck but the spleen was not palpable. Blood count revealed haemoglobin 86%, white cell count 8,600/mm.³, 54.5% lymphocytes and 12% atypical cells suggestive of 'blast' cells; platelets 4,500/mm.³ Sternal marrow examination did not substantiate a diagnosis of leukaemia and the Paul-Bunnell was positive, 1/640. Prednisone 20 mg. three times a day was started with immediate improvement in the extent of purpura although the Paul-Bunnell rose to 1/5120. Recovery was uneventful and 21 days after admission the patient returned to work taking prednisone 5 mg. twice a day. His blood count showed a normal differential white and platelet count. Paul-Bunnell was still positive, 1/640. Three months later prednisone was stopped as he had remained well with no purpura, but on 14.1.60 he again developed a purpuric rash in the presence of a negative Paul-Bunnell. Platelets were 136,000/mm.³ and prednisone therapy was recommenced. This patient still has a tendency to thrombocytopenic purpura which is controlled by small doses of prednisone. The Paul-Bunnell and white count remain normal 10 months after his admission, and there is no evidence of leukaemia.

Case 2

W.M., Male, aet. 40. Admitted 27.7.59

Eight days before admission this patient felt ill and feverish, finally developing jaundice. There had been no contact with chemicals or previous history of jaundice. On examination he was ill and jaundiced, with a few small cervical lymph glands and temperature 103.5°F. His tonsils were inflamed and covered with a grey membrane. The liver and spleen were not palpable. The urine contained bile. Blood count: haemoglobin 76%, white blood count 3,000/mm.³, polymorphs 92%. The bilirubin was 6.5 mg. %, but the only other evidence of abnormal liver function was a serum glutamic oxalacetic transaminase of 85 units. L.E. cells were not found in peripheral blood. The Paul-Bunnell was positive, 1/160, and subsequent white cell count five days later showed a white blood count of 7,200/mm.³, lymphocytes 53%. Other investigations were normal, and as his pyrexia continued with considerable malaise he was treated with prednisone 10 mg. four times a day; there was an immediate dramatic improvement, but this was not maintained after dose reduction, followed by cessation of steroid therapy 10 days later, the temperature rising to 100°F. diurnally and the malaise returning to a lesser degree. Reintroduction of prednisone in the original dosage once more resulted in complete recovery

and disappearance of the jaundice. Two months later he was well and at work, having had no treatment for three weeks; he remained so at the time of writing (20.6.60).

Case 3

E.C., Female, aet. 17. Admitted 22.9.59

Three weeks before admission she felt ill with headaches and lassitude, high fever, and apparent tonsillitis. She was treated by her doctor with a variety of antibiotics; the fever fell, but she remained ill with her throat still inflamed, and five days before admission began to sleep most of the time and could not walk unaided, her gait being severely ataxic. On examination she was afebrile, restless and dull mentally; the tonsils and fauces were anginous; there was discrete cervical and axillary lymphadenopathy and the spleen was just palpable. There was also gross dysarthria with bilateral intention tremor of the arms, and heel-shin ataxia of the legs. The pupils did not react to accommodation, but there was no neck stiffness and no pyramidal involvement. The blood count showed a total white cell count of $8,600/\text{mm}^3$ of which 66% were lymphocytes mainly of the glandular fever variety. The Paul-Bunnell test was positive, 1/1280. The cerebrospinal fluid was normal, as was serology for toxoplasmosis. Throat swab was negative for K.L.B. Treatment for four days with prednisone 20 mg. three times a day produced some improvement of the throat but none in the C.N.S. Initiation of 30 units ACTH twice a day brought about an immediate amelioration in the symptoms. The throat recovered quickly, and speech followed, but the neurological signs, in particular the loss of accommodation, improved over the next seven days. On discharge three weeks later she was symptom-free and there were no abnormal neurological signs. She was taking ACTH gel 20 units every other day on discharge and this was slowly tailed off without ill-effect. At the time of writing (20.6.60) she remains perfectly well and is having no therapy.

Case 4

F.B., Female, aet. 23. Admitted 10.6.58.

After 36 hours of malaise, vomiting, backache and abdominal pains this girl was admitted to hospital where her temperature was found to be 102.8°F . and there were several tender enlarged lymph glands in the right post-cervical triangle. The spleen was not felt. Blood count, haemoglobin 92%, white blood cells $2,600/\text{mm}^3$, of which 50% were lymphocytes, a small number being atypical. Paul-Bunnell was negative, as were blood cultures and Widal agglutinations. She continued to be unwell with a persistent pyrexia. The Paul-Bunnell became positive, 1/1280 on the seventh day. At this stage she was depressed, and still feeling extremely unwell. Prednisone 5 mg. four times a day was started with immediate return of the temperature to normal; the patient then felt completely well. Her recovery was maintained after the prednisone had been tailed off three weeks later. She remains well two years after this episode.

Case 5

M.S., Female, aet. 18. Admitted 27.6.59

This patient had a past history of sensitivity to penicillin and had been feeling unwell for two weeks; six days before admission she had felt feverish and ill with generalized aches and pains. On examination her temperature was 103°F . with an injected throat and several discrete lymph glands in both cervical groups. The spleen was not palpable. Paul-Bunnell was positive, 1/80. Blood count: haemoglobin 48%, white cell

count $2,800/\text{mm}^3$ with 30% lymphocytes and 13% abnormal cells which were considered probably to be atypical lymphocytes suggestive of glandular fever. Pyrexia continued and she remained unwell until the seventh day when the Paul-Bunnell had become positive, 1/320. Prednisone 5 mg. four times a day was started, with immediate relief of temperature and malaise. One month later the prednisone was tailed off and the patient continued to feel well. Her haemoglobin was 83% at this stage. At the time of writing, one year later she is well and working normally.

Case 6

S.W., Female, aet. 24. Admitted 23.3.59

One month before admission this patient began to have malaise, fever, lassitude, and sore throat. Two weeks later her Paul-Bunnell was positive, 1/80, and white blood count showed $14,000/\text{mm}^3$ of which 68% were lymphocytes. She rested in bed, but felt worse with nausea, vomiting and transient jaundice. She was admitted to hospital. On examination the temperature was normal with no abnormal physical signs except for some discrete cervical and axillary lymph glands. Paul-Bunnell was positive, 1/160. A.S.O. titre 100 units/ml. White blood cells $6,600/\text{mm}^3$ of which 43% were lymphocytes. Serum bilirubin was 0.5 mg. %. She complained bitterly of depression and lassitude although the temperature remained normal. She was treated with prednisone 5 mg. four times a day in view of her persistent malaise, and probable hepatitis. This resulted in considerable subjective improvement and she was able to return home within five days feeling normal, and taking a gradually reducing dose over the next month. She was well 14 days after discharge, and remains so one year later.

Case 7

J.G., Female, aet. 20. Admitted 30.7.59

This patient had had a sore throat, malaise, headache and fever for two weeks. She then became drowsy and developed an urticarial rash and loss of appetite. There was no previous history of allergic phenomena. On admission to hospital she was pale, with scattered cervical lymphadenopathy and a 'granular' pharyngitis. There were palatal petechiae. The spleen could be felt. Her temperature was 101°F . The Paul-Bunnell test was positive, 1/10,240. Blood count showed a white cell count of $10,000/\text{mm}^3$ of which 83% were atypical lymphocytes. Prednisone 5 mg. four times a day was started; the next day she ate a hearty breakfast for the first time since the onset of her illness and became interested in her surroundings; her temperature was normal. She was discharged home to continue with a gradually reducing dosage over the next month. With dose reduction her throat became anginous, and unfortunately her prednisone was stopped without our knowledge; it is probable that an increase in dosage would have considerably shortened her convalescence, which, however, differed in no way from that frequently seen in the untreated case. On 26.1.60 a Paul-Bunnell test was negative, in spite of a continued history of recurrent tonsillitis.

Case 8

G.B., Male, aet. 22. Admitted 25.5.60

This patient, with bilateral basal bronchiectasis, had been subject to recurrent chest infections for some time. Five days before admission he felt feverish and took terramycin for a self-diagnosed chest infection. He continued to be febrile and anorexic and had frontal headaches. On admission his temperature was 103°F . he had no dyspnoea or cyanosis and only minimal chest

signs. His spleen and cervical lymph glands were palpable, and the throat was injected. White cell count was 13,100/mm.³ of which 65% were lymphocytes, some typical of glandular fever. The Paul-Bunnell test was positive, 1/5120. He was treated with prednisone 5 mg. q.i.d. with immediate subjective improvement, and restoration of normal temperature within 12 hours. On discharge he was also given terramycin 250 mg. b.d. to avoid lung infection during the duration of steroid therapy. There has been no follow-up on this patient yet.

Case 9

E.D., Female, aet. 17. Admitted 20.5.60

This hard-working girl carried out a full-time job and looked after her father, brother and sister, keeping house for them. She had mumps four months before, but recovered well. Three weeks before admission she had a sore throat and pain in the neck, her face became swollen and she felt febrile and progressively unwell until she was unable to carry on. On admission she looked ill; temperature 101°F., with ulcerated enlarged tonsils and cervical lymphadenopathy. The spleen was palpable. Her face seemed slightly oedematous, but the urine contained no red cells or casts, and only a trace of albumen. White cell count was 7,800/mm.³ of which 78% were lymphocytes. Paul-Bunnell was positive, 1/640. Chest X-ray normal. She continued pyrexial for four days and was then given prednisone 5 mg. q.i.d. The temperature was normal in 24 hours and she felt much better. Two weeks later she was still well with no fever, or splenomegaly. She was discharged home on a decreasing dose of prednisone for one month. When last seen (21.6.60) she remained well. White cell count was 5,600/mm.³ with 42% lymphocytes, and Paul-Bunnell test was positive, 1/20.

Case 10

Male, aet. 24. Not Admitted

This patient, a doctor, began to feel ill on 14.3.60 with sore throat, general malaise and tender cervical glands. He found his work increasingly difficult and presented two weeks later. On examination there were tender cervical lymph glands and an inflamed throat. No spleen palpable. White cell count 11,400/mm.³, 85% lymphocytes. Paul-Bunnell was positive, 1/640. Throat swab grew staphylococcus aureus. He was given prednisone 5 mg. q.d.s. and tetracycline 250 mg. eight-hourly. There was a marked clinical improvement in seven days and the white cell count dropped to 5,200/mm.³, 67% lymphocytes. His progress was maintained whilst steroids were tailed off during the next seven weeks.

Discussion

It is not within the scope of this paper to discuss the aetiology of glandular fever. Many suggestions have been advanced, the most generally accepted aetiological theory being that of a virus infection, although no susceptible animal has yet been found; alternatively, it seems possible that there is an unusual tissue response to a variety of noxious stimuli, infective or otherwise. One of us (J.W.P.) has been impressed by the close time relationship of the disease to times of emotional and physical exhaustion, and it must be said that two of the patients in this series had recently become engaged and were about to be married, and experiencing considerable emotional pressure,

whilst two more were within a few weeks of being rebuffed during their first love affair. Case 5 missed an important examination through illness. Cases 9 and 10 were working extremely hard, one in unhappy circumstances, and one in a new environment. The background of Cases 1 and 2 were not investigated for possible stress factors.

As steroids have properties as 'antistressor' agents and promote lymphoid hypoplasia, and as no infective organism has been identified whose pathogenicity might be potentiated, it has seemed reasonable to use them in this condition, bearing in mind that the usual criteria must be fulfilled in making the diagnosis. There already appear to be five clear-cut indications for steroid therapy in glandular fever: hepatic complications, some anginose states, encephalitis, polyneuritis and thrombocytopenia. Severe cases of liver disease from various causes have been shown to respond dramatically to cortisone or corticotrophin. Case 2 is an example of severe liver involvement in glandular fever. Case 1 with thrombocytopenia responded equally well, although platelet agglutinins were not sought as in the case of Freeman and Wakefield⁴⁵; however, continuation of purpura with a negative Paul-Bunnell seems to suggest the presence of two antibodies. Case 3 presented with a severe anginose state complicated by encephalitic and cerebellar signs; though the throat condition improved on prednisone 20 mg. three times a day, ACTH was then started because of the severity of the neurological manifestations and previous experience of this agent in encephalitis. The result was impressive. Indeed, our experience suggests that there is no point in withholding steroid therapy in the really severe case of glandular fever whether there are complications or not, providing the usual contraindications to such therapy are observed. More controversially, we suggest that steroids seem to be beneficial in the treatment of those patients with the uncomplicated disease who continue with pyrexia and malaise after the usual period of bed rest, or in that large group of patients with glandular fever whose convalescence can be so very slow. Such patients show few physical signs, but look ill and feel worse for many weeks. Examples of response by this form of the disease are demonstrated by Cases 4, 5, 9 and 10. It appears that a month's treatment with prednisone on a reducing dosage may do much for this group, possibly by helping to suppress the hidden hepatic complication demonstrated by liver biopsy, and believed to be so prevalent even without jaundice.⁸ Follow-up of Cases 1-7 has shown that only Case 1 has required continued prednisone therapy, and this for thrombocytopenia. There is no evidence of leukaemia. Case 7 has had recurrent tonsillitis although her Paul-Bunnell and white count were

normal, and this symptom cannot be attributed to continuing glandular fever. Cases 8 and 9 have been included to show the dramatic effect of prednisone subjectively and on the pyrexia, but they are too recent for continued improvement to be reported. We can vouch for the good health of Case 10 who is a medical colleague.

Dosage

Our patients usually started with between 20-60 mg. prednisone daily in divided dosage, to be reduced slowly over the next few weeks. Case 3 might have responded to continued prednisone but we felt bound to change to ACTH for the reasons stated. The apparent superiority of ACTH over oral steroids here, and in other diseases such as ulcerative colitis, may well lie in the matter of effective dosage rather than any specific therapeutic effect. We consider that some authors have not used a sufficient initial dose, nor have they continued the therapy for long enough, and for this reason we would not agree with Mason and Adams⁷ that the speed of recovery is similar to those cases treated with bed rest only. We also feel that the dosage should be lessened slowly, and Cases 2 and 7 demonstrate the relapse which occurs if the drug is withdrawn too quickly.

Until more is known of the cause and mechanisms involved in glandular fever, any interpretation of the apparent beneficial effect of steroids in the treatment of the disease, especially of its complications, can be no more than conjecture. We suspect

that the benefit may arise from the known hypoplastic effect of steroids on lymphatic tissue, on hepatitis and encephalitis, as 'antistressor' agents, and possibly by reduction of unhelpful antigen-antibody responses.

Summary

Ten patients with glandular fever are reported in whom steroid therapy had a beneficial effect; three of these had severe complications.

The indications for steroid treatment are discussed together with suggestions for effective therapy.

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