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RÉSUMÉ

On sait, depuis les travaux de Lacassagne, que les œstrogènes favorisent le développement des fibromyomes utérins chez certains animaux de laboratoire. 130 femmes porteuses de fibromes utérine prises au hasard furent étudiées attentivement, et leur histoire révèle chez 52% d'entre elles un épisode ménorrhagique entre 10 et 20 ans, tandis que 63% étaient des hypothyroidiennes. On sait que les ménorrhagies fonctionnelles et l'hypothyroidie sont souvent contemporaines des dosages élevés d'œstrogène dans l'organisme. Pour conséquent, les fibromyomes humains seraient peut-être d'origine horminale. Si cette hypothèse se vérifie, la prophylaxie des fibromes serait assurée par l'administration d'extrait thyroidien et de vitamine E, qui sont tous deux fortement antiœstrogéniques. JEAN SAUCIER

TOXIC HEPATITIS IN FEVER THERAPY

By Surgeon-Lieutenant Robert M. MacDonald, R.C.N.V.R.

FEVER therapy has established itself as a useful form of treatment in a number of diseases, especially neurosyphilis and in sulfa-resistant gonorrhœa. Prior to the introduction of penicillin, it was considered by many as the routine treatment for the latter disease. It is generally accepted as a relatively safe procedure if it is carried out in a well equipped clinic with experienced staff. Among the complications of artificial fever, jaundice is mentioned as a rare one and only occurring in cases of marked circulatory collapse, dehydration, or with low blood chlorides. This has not been our experience. We have encountered 48 cases in 250 patients treated for sulfa-resistant gonorrhœal infection in healthy young men. This is an incidence of 19.2%. Until the recent paper by King, Williams and Nichol,[1] and the related paper on physiological and biochemical changes following fever therapy by Wallace and Bushby,[2] no reference has been found of a comparable incidence of jaundice in such patients. On discussing the problem with several other workers in Canada, I have been informed that it is not infrequent in their clinics.

Before discussing these cases, it seems advisable to outline our treatment routine. The patients were Navy, Army or Air Force personnel, who have been considered sulfa-resistant gonorrhœa and have been referred to us for fever therapy. They have been a very co-operative group and little difficulty was encountered in the administration of treatment. They were admitted to our hospital 2 days before treatment for investigation and examination. During these days they received ordinary diet, extra fluids, salt capsules of 1 gram 4 times daily, vitamin B_1, 18 milligrams daily and intramuscular vitamin B complex (beminal) ¼ c.c. daily. In the 12 hours preceding therapy they were given 6 gm. of sulfathiazole or sulfadiazine if there was no history of toxicity. Special attention in familiarizing them with the nature of the treatment was found to be of great psychological help.

The induction period lasted about 1¼ hours to reach 106°. Treatment consisted of 7 hours above 106° and we endeavoured to keep the rectal temperature at 106.7°; care was taken that the temperature did not exceed 106.8°. Intravenous drip of 5% glucose in saline was routine after induction. Originally 1,000 c.c. was given but about ¾ of the cases had 2,000 c.c. over a period of 3 to 6 hours, usually about 5 hours. This was supplemented by oral water or dilute 0.3% saline. Three or four injections of 50 c.c. of 50% dextrose or sucrose were given during treatment. Oxygen by means of a nasal B.L.B. mask was administered for 20 to 60% of the treatment period. Pantopon grain 1/3 was usually given during induction and at times a supplementary dose of grain 1/6 was given in the latter half of treatment. No sedation was used prior to admission to the cabinet.

On return to the ward patients were allowed fluids, but no attempt to force fluids was made for several hours. They were permitted bathroom privileges the next forenoon if the systolic blood pressure was over 100 and the patient felt well enough.

They were allowed up 24 hours after treatment if their general condition was satisfactory. In the days following the treatment fluids were forced and diet was modified according to their desires. Poor fluid intake, moderate vomiting, dehydration or evidence of circulatory collapse were treated by intravenous

therapy. Intake and output of fluids were not recorded in the majority of cases and decision as to dehydration was based on known vomiting, estimated intake, general condition of skin and tongue and urine specific gravity.

The cabinets in use were a D.P. and N.H. standard which are simple in design and have a fan behind a 2 element heating unit. The hot air is blown over a pan with wick towelling and results in highly saturated warm air which circulates up the sides and the foot of the mattress to the main body of the cabinet.

Brief consideration of the whole series is thought desirable before analyzing the jaundice cases. The 250 cases were consecutive ones. Two other patients, one with psychogenic tachycardia and the other unco-operative, were in the cabinet so short a period that they have not been included. One hundred and ninety-five patients had 1 session, 41 had 2 sessions, 12 had 3 sessions and 2 had 4 sessions of fever. In the series there were 21 patients who were removed from the cabinet before completing their 7 hours and 12 of these had less than 5½ hours. Treatment was stopped for tachycardia, excessive vomiting, temperature rising above 107° or delirium. One of them had convulsions at a temperature under 107° and no further attempt at treatment was made. Of those having less than 5½ hours of treatment, 3 resulted in a cure, while the remaining 8 had an uneventful second session. Of our whole series of 250 cases, there were no patients who refused a second or third session when we considered it advisable.

Of the 246 cases of gonorrhœal urethritis, we have had 9 failures, and 4 of these were in the group of 16 sulfa toxic patients who received fever without chemotherapy. Our apparent cure was 97.8% in the 230 cases who had our routine fever plus sulfonamide. Criterion of cure was based on disappearance of urethral discharge, negative under smear and culture and urine examination. There were 2 known relapses, one responding to another course of sulfonamide and the other to penicillin. It is estimated that 25 to 50% of our cases would be away from this area 1 month after discharge from hospital, so subsequent relapses, if any, in this group would be unknown to us.

INCIDENCE OF JAUNDICE

In our jaundice series of 48 cases, 5 patients were considered marked jaundice, 6 patients moderate and the remaining 37 were mild or doubtful. Any of the doubtful cases had a raised icteric index usually about 15 to 20. With the exception of 4 mild but definite cases all other cases considered in this series had serum bilirubin investigations. As a rule any cases with an icteric index of 15 to 20, had a negative or slightly positive direct van den Bergh reaction while those above 20 were almost invariably positive direct.

Clinical icterus was usually detected on the 2nd or 3rd day after fever. Occasionally it was seen on the 1st day and sometimes not until the 4th day. In cases not noted until 2nd or 3rd day, a raised serum bilirubin was usually present on the 1st day. One example of a mild clinical case had the following icteric indices, 1st day 10, 2nd day 22, 3rd day 28, and 6th day 19. One case with icterus visible in the sclera on the 1st day after fever had an index of 38 with a positive direct van den Bergh. He subsequently developed a marked jaundice although he never appeared very ill. In only a couple of cases was the liver considered enlarged and never greatly so. Tenderness in the liver area was encountered a few times but one was impressed with the negative physical findings in the majority of cases. Two patients stated they passed several pale stools but these were not examined. The first urine was a positive test for urobilinogen and followed by bile. In those with marked jaundice and larger amounts of bile in the urine the urobilinogen was reduced or absent. In most of the cases the abnormal urine findings were of short duration as was the jaundice.

There were no cases of definite bradycardia noted although in most of the cases of marked jaundice there were pulse recordings of 56 to 70 for 1 to 2 days, in the period of 5 to 10 days after treatment when they were showing great clinical improvement. The more usual finding was a slightly increased pulse rate and in a moderate number there was a mild pyrexia of 99 to 100° for 1 or 2 days and occasionally longer.

In 2 of our earlier mild cases where a cure did not result in the session we repeated it in about 10 days' time with no ill effect or recurrence of jaundice. In 2 other more recent cases we referred them for penicillin although they were no worse than the first 2 failures on one session. The remaining 44 jaundiced pa-

tients obtained an apparent cure with one session.

Cases of Marked Jaundice

These cases had an average intravenous intake of 1,900 c.c. of 5% glucose in saline. In 4 of the 5 cases treatment was uneventful with no vomiting, while the fifth case had considerable vomiting of clear fluid and was confused during part of his treatment. This case required active treatment for marked circulatory collapse soon after his return to the ward. The case referred to above with an icteric index of 38 on the day following treatment, was one who had an uneventful 7 hour session, had no vomiting during treatment nor during the night following it and was feeling fairly well the next day when icterus was noted. Subsequently, he had moderate nausea and vomiting for several days but never appeared dehydrated nor looked seriously ill. He was one of a considerable group where the nausea and vomiting appeared to be the result of his toxic hepatitis rather than the cause. Another of these marked cases was uneventful until 24 hours after fever therapy when nausea and vomiting began and on the following morning icterus was visible and he had an index of 66. This patient's condition became worse and reached its peak on the 5th day with signs of cholæmia. Following this alarming state he improved steadily but still had an icteric index of 37 on the 17th day after his fever. This patient and the one with the marked circulatory collapse were the only ones whose condition appeared serious. We have had no fatalities at our clinic up to the present time.

Cases of Moderate Jaundice

Of the 6 cases in this group only 1 vomited during treatment and that was but once. The average amount of intravenous 5% glucose in saline was about 1,500 c.c. Two of these were confused during part of their session but otherwise their condition was satisfactory, while the remaining 4 cases had uneventful treatments. Following treatment one patient had no vomiting, 4 patients had moderate amount of nausea and vomiting, and the 6th case had marked vomiting and a 2nd degree burn of his shins.

Cases of Slight Jaundice

These cases, 37 in number, were not obviously different from many non-icteric cases and could easily be missed if not looked for carefully. Most of them had an uneventful treatment and averaged nearly 2,000 c.c. of 5% glucose in saline intravenously. Following treatment a few had no vomiting, a few had marked vomiting but the majority had moderate nausea and vomiting for 1 to 3 days.

In considering the whole series of 48 cases of jaundice there are certain points that stand out. In the majority the treatment was uneventful although in some cases restlessness or even confusion at times was noted. In 30 cases no vomiting occurred during treatment and only 4 cases vomited more than twice. This compares favourably with the non-jaundiced group. The vomiting after treatment was more marked in the jaundiced patients but there were many cases with similar degree of nausea and vomiting who did not develop jaundice. Once again it is stressed that the clinical impression was that much of this vomiting was due to the hepatitis and not the cause of the jaundice. Herpes was noted in 60% of the cases, an identical figure to that of the non-jaundiced patients. This figure includes very mild herpes and some with no skin lesions but only inside the mouth. In the second half of our series the vitamin B premedication was discontinued to compare its alleged effect in the prevention of herpes. A slight increase was noted in the second half but it is of doubtful statistical significance.

There was no difference in the jaundice incidence in the cases receiving vitamins of the dosage given by us. In the earlier cases of our series we did not use any coverings except a jock strap and we found, contrary to some other clinics, that we were troubled with blisters of the feet in quite a few cases and we had three cases with burns of the shins which required remaining in hospital for treatment of the burns. Since we began oiling the feet and legs and covering them with terry cloth stockings we have had nothing more serious than mild blisters of one or more toes. It seems probable that the cause of the burns is the rather excessive heat at the foot of the cabinet if both heater elements are on, as our nurses did not have any trouble with burns in other cabinets of essentially the same construction with which they worked previously.

The first half of the cases was receiving sulfadiazine but it was then changed to sulfathiazole to see if there would be any lowering of the incidence of jaundice. No appreciable difference was noted.

Discussion

The incidence of jaundice in our series is rather startling in view of the scarcity of references to the subject in the vast literature on fever therapy. It seems reasonably certain in view of the clinical picture, icteric index and urine findings that the majority of these cases do not suffer any irreparable liver damage. However, it is not so easy to be dogmatic in the cases of more severe and prolonged jaundice even though they made an uneventful clinical recovery. The possibility of permanent liver damage and knowing about several cases of death from acute liver necrosis following fever therapy makes one feel that this subject of hepatitis is deserving of more study.

It is generally known that in severe shock, such as in the one case of ours described above, jaundice may occur. Whether it is due to circulatory collapse or anoxia or both is not certain. There is a possibility of the mechanism of this syndrome, heat exhaustion, heat stroke, acute liver death and toxæmia of burns having features in common. However, one feels that the clinical picture was so different in that one case that it is probably more profitable to study the remaining 47 cases which had jaundice and were clinically more alike.

Anoxia may play some part in the etiology but Wallace[2] found jaundice in a series in which oxygen had been used continuously, and some clinics use no oxygen therapy and have not been struck by their incidence of jaundice. We believe that more extensive use of oxygen than has been our practice is probably desirable but cannot feel that this is the chief factor in the production of our jaundice.

We believe that the current American belief of the fluids and chloride etiology of jaundice is not proved. Our blood chloride analyses were not numerous enough to draw conclusions from, but when one considers the quantities of salt and fluids given before, during and after treatment, they are equal to or more than in the average fever therapy clinic. The statement of some people that on the appearance of early icterus an intravenous administration of saline will quickly result in its disappearance, is not in agreement with our experience. Some cases proceed on to moderate or marked jaundice even though intravenous therapy is started early, while most of the mild cases are very fleeting and soon disappear even without intravenous saline.

The blood counts and associated investigations of Wallace were against an hæmolytic origin of the jaundice. Our van den Bergh reactions and urine findings support this and point to a liver cell damage.

One of the first thoughts we had on encountering the early cases of jaundice was the possibility of fever activating a latent infective hepatitis but on studying the series one is impressed by the rapidity with which a marked icterus may appear, and it seems improbable that an infective hepatitis could be so accelerated.

A similarity in some respects was noted between our cases of jaundice and the toxæmia of burns which occurs 1 to 5 days after the burn and is accompanied by nausea, vomiting, slight pyrexia and in some cases jaundice. Although some authors state that jaundice in burns is rare, Wilson,[3] in his series noted 12 cases of jaundice in 65 serious burns and felt it would have been higher if closer observation was made in the earlier cases. The toxæmia of burns is usually seen in severe cases but not invariably so. The question of an actual blood circulating toxin in burns has much to support it but some authorities claim it is not yet proved and the recent work on the effects of tannic acid as a cause of liver necrosis will make the supporters of the toxæmia theory less secure. The fact that our cabinets were simple in design and that it was not as easy to prevent superficial burns as with more elaborately constructed cabinets led us to give thought to the possibility of a "toxæmia" theory of hepatitis. Such a theory would postulate a toxin resulting from a large area of skin being subjected to a relatively hot atmosphere for a period of about 8½ hours. Any such theory would require such a toxin being formed without the necessity of blister formation, as the percentage of jaundiced cases with blister formation was not appreciably greater than in the whole series. There is little evidence to support this hypothesis and one would have expected more jaundice in the older radiant heat cabinets which did not have the humidity of our modern apparatus.

We now come to what appears as the most probable main factor in the etiology of our jaundice, namely the direct effect of the high body temperature on the liver in patients who have a relatively high blood sulfa level. Although few clinics have been administering temperatures of 106.7° in the recent years, in treatment of neurosyphilis, there must have

been thousands of patients treated at such a temperature in the last 10 to 15 years and an incidence of jaundice such as we observed would have been noted in early years. In our limited experience of neurosyphilis treatments at about 105° we have never noted any jaundice. Of our 16 sulfa toxic patients who received fever therapy without chemotherapy none of them developed clinical jaundice but one had an icteric index of 20 on the first day after fever and is included in our jaundice series. The group of cases without chemotherapy is too small to draw any conclusions from but it is suggestive. The fact that in the 21 cases whose treatment was terminated before 7 hours was completed no jaundice was noted, is suggestive of length of fever having a bearing on the question and especially as these incompleted treatments were made up of patients who had delirium and other evidence of anoxæmia or cerebral œdema, and in some cases marked vomiting following removal from the cabinet. Wallace states that sulfonamides do not increase the hazards, including jaundice, of fever therapy. He found a bilirubinæmia in cases given fever without sulfonamides but does not state when the previous drug administration was stopped. Most, if not all, of his subjects were sulfa-resistant gonorrhœa.

Among the toxic effects of the sulfonamides liver damage is generally considered an infrequent one. Nevertheless a considerable number of cases of toxic hepatitis from these drugs has been reported. Sulfanilamide is more toxic than sulfapyridine, while sulfathiazole and sulfadiazine would appear to be less toxic. Geever[4] has recently reported on 2 fatal cases where the predominating pathological lesion was a liver damage attributed to sulfadiazine. Cantarow and Wirts,[5] in their article on hyperbilirubinæmia following sulfonamide administration, quote cases of liver damage attributed to the drugs and they believe that routine determination of serum bilirubin and tests of hepatic function would probably reveal a much higher incidence of hepatic functional impairment than has been reported. With such evidence of potential or actual liver damage it does not seem strange that this injury could be aggravated by the abnormal temperature during fever therapy, which must in itself put a strain on an organ so intimately concerned with metabolism. This theory of the etiology of our toxic hepatitis appears most plausible but further proof is still necessary.

The more satisfactory results of the combination treatment of fever and sulfonamides makes one hesitate to discontinue the use of chemotherapy with fever and we have adopted the advice of King and are giving large amounts of protein for 2 days before treatment and aiming at keeping the patient's temperature at 106.0° as well as the more liberal use of oxygen. The increased protein diet as a liver protective has arisen out of the work of Whipple and his associates and the numerous experimental and clinical reports which have appeared in the last few years.

SUMMARY

1. A review of 250 consecutive cases of gonorrhœal infection has been made.

2. Jaundice was present in 48 cases, giving an incidence of 19.2%.

3. A discussion of possible etiological factors has been attempted.

4. It is suggested that this condition is a toxic hepatitis largely resulting from the effect of the high fever on a body with a relatively high blood level of sulfonamide.

My thanks are due to Dr. C. Macleod, Chief Medical Officer of Camp Hill Hospital, Halifax, the nursing staff of our fever therapy clinic and ward and to Surgeon Lieutenant W. J. Elliott, who was associated with me in this work.

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