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EFFECT OF VITAMIN B₁₂ ON NEUROPATHY IN PERNICIOUS ANAEMIA TREATED WITH FOLIC ACID

BY

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The remarkable effectiveness of vitamin B₁₂ in severe lesions of the central nervous system caused by folic-acid treatment of pernicious anaemia is well illustrated by the record of a patient who came recently under observation.

Case Report

A woman aged 74, whose previous history was one of good health, developed lassitude and dyspnoea on exertion about three years ago, when pernicious anaemia was diagnosed and confirmed by blood examination. Concentrated liver injections were given. After the third injection she developed a sensitization dermatitis, for which she was admitted to the skin department of a hospital on February 15, 1948—that is, four months after the onset of the skin disease. Apart from the dermatitis she appeared to be in good health and the case report did not record any neurological disorder. Her blood count on February 18 was: red cells, 3,690,000; white cells, 8,650; haemoglobin, 80%; colour index, 1.1. Her skin condition cleared up with local application and x-ray therapy, and she left hospital on February 25 with a haemoglobin level of 99%. Whilst in hospital, liver injections were stopped and she was put on 15 mg. of folic acid daily, which she had taken until her admission to this hospital.

In May, 1949 (after 15 months' folic-acid treatment), she complained of weakness and unsteadiness of her legs and loss of appetite. From August her diet consisted of bread, margarine, butter, and tea. She had an egg on rare occasions, but took practically no vegetables, meat, or fish. Towards the middle of October she became mentally deranged, bed-ridden, and incontinent.

On admission to the medical division of Newsham Hospital on November 8 her condition was as follows. She lay in a curled-up position, unable to give any history. She was disorientated about place and time, extremely restless, incontinent, delusional, and very dirty in her habits. There was no gross wasting. The skin was dry, with a scaly papular dermatitis of the lower third of both legs. There was angular stomatitis, and the tongue was glazed and beefy. The lymph nodes were not enlarged. Fibrillation was present. B.P. 90/60; chest clear. There was no enlargement of liver or spleen and no tenderness or any mass in the abdomen. The urine was normal. A blood count showed: red cells, 3,500,000; haemoglobin, 78%; colour index, 1.1; M.C.D., 7.8 μ (Eve). White cells, 4,000; lymphocytes 2,150 (54%), monocytes 50 (1%), polymorphonuclears 1,700 (42%), eosinophils 100 (3%). The blood film was consistent with treated pernicious anaemia.

Examination of the nervous system revealed no disorder of the cranial nerves, and the fundi were normal. Investigation of the upper limbs showed gross ataxia, brisk tendon reflexes, Hoffmann's sign present on left side, impaired superficial sensation, joint and vibration sense lost, and muscular power not grossly impaired; the abdominal reflexes were absent. The lower limbs showed gross ataxia, brisk tendon reflexes, bilateral extensor response, impaired muscular power, loss of vibration sense and joint sense, impaired sensation for touch and pain.

A diagnosis was made of neuropathy following folic-acid treatment of pernicious anaemia in a woman who also suffered from nutritional (vitamin B) deficiency.

On November 15, 2 ml. of "cytamen," containing an equivalent of 40 μ g. of vitamin B₁₂, was injected. Subsequently 1 ml. was injected every third day until December 1, every fifth day until December 13, and every seventh day afterwards until February 28, 1950, when she was put on fortnightly injections of 2 ml. The total dose of vitamin B₁₂ given was 0.5 mg.

Progress.—For five days she had to be fed on fluids only. Her appetite returned after the second injection. She remained incontinent until December 12, by which time she could sit on a chair. Towards the end of December walking exercises were started. On January 5 the ataxia of her upper limbs had disappeared. The reflexes of her lower limbs were still brisk and there was an extensor response on the left side. Superficial and deep sensation were both impaired in her legs. Her mental condition had greatly improved, and she was able for the first time to give a clear history of herself except for the period after August, 1949.

On January 21 the case record states: "Mentally alert and rational; lively sense of humour. Upper limbs—no weakness of either hand. Reflexes brisk; no impairment of superficial or deep sensations; vibration sense normal. Finger-nose test normal. Lower limbs—brisk tendon reflexes. Bilateral flexor response—some impairment of sensation to cotton-wool and pin-prick. No loss of muscular or joint sense. Vibration sense absent. Heel-knee attempt still poor. Gait unsteady but not spastic."

On February 7 she walked without help and was quite steady. There was still some impairment of deep sensation. On February 14 she walked quite normally and climbed two flights of stairs unaided. Her physical and mental condition was good. Blood examination showed normal values from December 13 onwards. The patient left hospital in March with a recommendation to her doctor for maintenance doses of 40 μ g. vitamin B₁₂ every fortnight.

Discussion

The above case record confirms the dangers of folic-acid treatment of pernicious anaemia pointed out by Israëls and Wilkinson (1949). The patient, who had had no previous neurological lesion, developed a severe neuropathy involving the brain, spinal cord, and peripheral nerves, in the fifteenth month of folic-acid treatment, during which period her blood remained at a fair level. The resulting psychosis and the neurological lesions were promptly arrested by

vitamin B₁₂ and fully restored within three months, a period which, in an aged patient, seemed to be extraordinarily short.

Our observations confirmed the experiences of Berk *et al.* (1948), Hall and Campbell (1948), Hall *et al.* (1949), Mollin (1949), and Ungley (1949), who found vitamin B₁₂ effective in the treatment of neurological complications of pernicious anaemia.

Summary

A case of severe psychoneuropathy in the course of folic-acid treatment of pernicious anaemia is reported.

Its complete and rapid restitution with injections of vitamin B₁₂ is described.

My thanks are due to Glaxo Laboratories Ltd. for the generous supplies of cytamem.

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Medical Memoranda

Prolonged Retention of Dead Foetus in Utero

A report of the following most unusual case is worth recording.

CASE REPORT

A Chinese 3-para, aged 47, was admitted to hospital on January 4, 1950, complaining of an abdominal lump which had been present for over two years, and weakness and inability to leave her bed for two months. She had been pale for five months. Her youngest child was aged 20. In August, 1946, she became pregnant and, apart from the fact that the size of the abdomen led to a suspicion of multiple pregnancy, the antenatal period was uneventful. At term, in May, 1947, there was a little vaginal bleeding and she had pains resembling those of labour. Foetal movement ceased, the membranes did not rupture, and nothing was expelled. Menstruation returned and was normal and regular until four months before her admission to hospital. The abdomen varied in size, being smaller when the periods were regular and increasing when they ceased. There was some upper abdominal pain.

The patient was thin and pale, and looked ill. Her temperature was 97° F. (36.1° C.), pulse 78, and respirations 20. Her blood pressure was 82/58. The heart and lungs were normal. An abdominal tumour the size and shape of a 28-weeks pregnant uterus was found. It was much firmer than an ordinary pregnant uterus, but neither hard nor fluctuant. It was tender, fairly fixed, and resonant to percussion. There was shifting dullness in the right flank, but resonance in the left, even when the patient was lying on her left side. Vaginal examination revealed a firm effaced cervix with a closed external os and a hard mass like a small foetal head above it. The abdominal mass seemed continuous with the uterus. At a later examination it was thought that foetal parts could be palpated.

The urine was acid and contained albumin, a few pus cells, and red blood cells. A blood count showed: white cells, 15,850 (neutrophils 81%, lymphocytes 17%, monocytes 3%); red cells, 2,710,000; haemoglobin 52%. The Kahn reaction was +.

The patient was kept under observation for nine days, during which efforts were made to secure donors for blood transfusion. These were not forthcoming. Many of the Chinese peasants look upon their blood as their life, and do not feel called upon to give it even for a relative. In this case, however, the husband and daughter were willing, but were unsuitable. Eventually a lady missionary with poor and much-covered veins, but com-

patible blood, volunteered. Only a small volume was obtained, and this was given to the patient, whose condition was deteriorating. Her red count had fallen to 1,670,000 and her haemoglobin to 28%. She had spells of vomiting and was irrational in the evening. In spite of a warning that a fatal issue was likely, the relatives desired operation.

On January 13, using a rectus sheath field block and a small amount of intravenous thiopentone, a lower midline abdominal incision was made. Adhesions were so dense and extensive over the tumour that it was difficult to tell when the peritoneal layer had been penetrated. The incision was extended beyond the umbilicus in an unsuccessful endeavour to get above the adhesions. Palpation of the mass at this stage revealed unmistakable foetal parts, so the uterus was opened vertically. It contained a putrid mass comprising an apparently full-term foetus considerably decomposed. This was removed almost intact. There was some slight retraction of the uterus in the upper part only. On the lower posterior wall, and apparently covering the internal os, was a leathery mass which was taken to be the placenta, but as the patient was unable to stand further blood loss no attempt was made to disturb it. The uterus was irrigated with saline, a drainage tube was inserted, and the uterus and the abdominal wall were closed. Intravenous saline was administered throughout the operation and the patient was returned to bed in fair condition.

Next morning her condition was still fair, and there was a copious foul seropurulent discharge from the drainage tube. Through this, using a two-way metal catheter, a continuous drip lavage was instituted, but the patient gradually lapsed into coma and she died 40 hours later.

COMMENT

The special interest in this case centres round the length of time the dead foetus remained in the uterus. The dates given were according to the Chinese calendar, but there is no reason to doubt their accuracy. The positive Kahn test could account for the death of the foetus, but it is difficult to know why labour did not continue, and why there was not more distress at the time.

Many points made diagnosis difficult. The age of the patient, the fact that she had not been pregnant for 20 years, the length of time since the alleged pregnancy, and the history of subsequent normal periods made it hard to believe that she had been pregnant in 1946. The resonant percussion note with absence of bowel sounds over the tumour was puzzling. It was no doubt due to putrefactive gases in the uterus, though there was no special rush of these when the organ was incised. At the time of operation the provisional diagnosis was infected uterine fibroids.

The cause of death was not quite clear. It was to be expected that the patient would succumb during or soon after the operation, but her condition next morning was quite satisfactory. No facilities were available for blood chemistry tests, but the absence of any other obvious cause of coma suggested uraemia. This could have resulted from amyloid changes in the kidney after the long period of septic absorption. The vomiting and mental confusion prior to operation would support this diagnosis. No post-mortem examination was possible, as this procedure is unknown in rural China.

Mention might be made of the use of the rectus sheath field block anaesthesia according to the technique advocated by Minnitt and Gillies (1948). Owing to its easy administration and its complete lack of after-effects this has been found most satisfactory when patients are apparently *in extremis*. The relaxation it provides is fully adequate.

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