HUMORAL EFFECTS OF METASTASIZING CARCINOID TUMOUR

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The syndrome associated with malignant carcinoid tumour with hepatic metastases has only been recognized fairly recently, the first case being described by Sir Maurice Cassidy (1930). The clinical manifestations are thought to be due to the secretion of 5-hydroxytryptamine (serotonin) by the tumour and its metastases (Thorson et al., 1954).

Case Report
The patient, a male aged 55 years, was admitted to hospital with severe watery diarrhoea and vomiting, which had lasted for several hours. His symptoms disappeared shortly after admission, without specific treatment. He gave a history of intermittent diarrhoea for the previous 12 months, with four severe attacks in the last three months. There had not been much weight loss and the appetite was good. The attacks began with flushing of the face and neck, sweating, and diarrhoea, and lasted on average three to four hours. Occasionally vomiting occurred but there was no abdominal pain. Sometimes tingling of the fingers and muscle cramps were experienced.

On examination, the general condition was good. The abdomen was rather distended but no other abnormality was noted. Rectal examination was negative, as were a sigmoidoscopy, chest X-ray, and barium enema. Barium meal X-ray showed delayed emptying of the stomach—a residue being still present at 48 hours—but no other abnormality.

He was discharged after three weeks, and was again seen as an outpatient six weeks later, when he was still complaining of loose motions. Abdominal examination was negative, apart from some gaseous distension. Sugar was found in the urine, and he was admitted for further investigation. A Glucose Tolerance Test showed a normal fasting blood sugar (80 mg. per cent.), but impaired carbohydrate tolerance, the blood sugar at two hours being 242 mg. per cent. No pathogenic organisms were isolated from the faeces, and microscopy was negative apart from the presence of a few partially-digested muscle fibres. A fractional test meal showed a small amount of free acid after histamine. Serum amylase was 249 units, and blood W.R. negative.

The patient had no symptoms during two weeks’ stay in hospital on this occasion, and insisted that he felt perfectly fit, but two days after discharge he had a further attack of diarrhoea and vomiting, and was re-admitted. His symptoms subsided soon after admission, and he was symptom-free for three weeks, and then developed severe watery diarrhoea and repeated vomiting, accompanied by collapse—three hours after the attack began the radial pulse was almost imperceptible and the blood pressure fell to 50/0. Vomiting continued—about four pints in four hours—in addition to diarrhoea. Intravenous saline drip and hourly aspiration of the stomach brought about an improvement in his condition, and the next day he had no symptoms, though there was still a tachycardia (rate 120 per minute). After a further 24 hours complete recovery had taken place, and the heart rate had fallen to 70 per minute.

Eleven days later he had an attack of flushing of the face but no diarrhoea, and four days after this, flushing, diarrhoea, and vomiting again developed, with severe collapse. At the height of the attack the blood pressure was unrecordable by sphygmomanometer and the radial pulse was not palpable; the femoral pulse was easily palpable at a rate of 120 per minute. He was fully conscious and rational in spite of the fact that the brachial blood pressure was unrecordable. He recovered on treatment with intravenous saline and gastric aspiration, and remained fairly well for the next two weeks, when he had another severe attack in which the blood pressure could not be recorded. In another episode three weeks later, noradrenaline was used successfully to correct the hypotension.

Many other investigations were carried out at this time, including X-ray of the skull and long bones, intravenous pyelogram, electroencephalogram, and examination of the duodenal juice for trypsin, all of which showed no significant abnormality.

At laparotomy by Mr. R. W. Doyle, both lobes
of the liver appeared to contain massive deposits of carcinomatous tissue. Some enlarged glands were seen in the right side of the gastro-hepatic omentum and one of these was taken for section. Some small nodules were also seen near the coeliac axis, and one of these was also removed, and a biopsy of the abnormal liver tissue was made. His immediate post-operative condition was satisfactory, but he later deteriorated and death occurred on the day after operation.

At autopsy by Dr. W. K. McGinley, the right lobe of the liver was found to be totally infiltrated with secondary malignant tissue. The left lobe was free from growth. The left adrenal gland contained a small fleshy growth in its medulla, and the para-aortic glands were infiltrated. All other organs appeared normal, and no primary tumour was found in the intestine.

Professor A. C. P. Campbell reported as follows on the histological sections: 'The general morphology in haematoxylin and eosin sections is certainly compatible with a malignant carcinoid... We have persistently had a negative result with the tumour cells with the Alkaline Diazo method, and with the Masson-Fontana method (Hamperl's procedure). So I think one must say that the tumour shows no sign of differentiated argentaffin cells. On the other hand, with Bodian's Protargol method a few of the tumour cells do show undoubted argyrophil granules... If this is a case of the 5-HT syndrome, it would not be the first in which tumour cells had failed to give the histochemical reactions of differentiated argentaffin cells.'

Discussion

Unfortunately, as the diagnosis in this case was not considered during life, no estimation of 5-hydroxytryptamine in the serum or urine was made. However, in view of the histological appearance of the tumour cells, and the characteristic symptoms of flushing of the face, vomiting, and severe diarrhoea, it seems fairly certain that this was a case of malignant carcinoid tumour giving rise to humoral effects. An outstanding feature of the attacks was the severe circulatory collapse, and in this respect the case was similar to that described by Snow et al. (1955, Case 2). These authors point out that such circulatory collapse has not previously been described in the 5-HT syndrome, though they mention that in animal experiments with 5-HT, hypertensive, hypotensive, or mixed responses are seen. In man, the intravenous injection of 5-HT leads to a rise in blood pressure (Page and McGubbin, 1953), and in the case being reported here it is possible that the circulatory collapse may have resulted solely from the severe and rapid fluid and electrolyte loss due to vomiting and diarrhoea.

Another interesting feature of the attacks was the clear mental state in the presence of circulatory collapse of such severity that the brachial blood pressure was unrecordable and the radial pulse not palpable, the patient being able to carry on a rational conversation whilst in this state. Snow et al. (1955) noted the fact that in their Case 2 consciousness was retained in all but one of 12 attacks in spite of the fact that no peripheral pulse could be felt, even in the carotid arteries. In the algid or collapse stage of cholera the pulse may disappear completely at the wrist, and the systolic blood pressure may fall to 40 to 70 mm. Hg., but despite this circulatory collapse, the mind generally remains clear (Hamilton Fairley, 1956); but it must be extremely rare for consciousness to be retained in the absence of recordable blood pressure, especially if this state continues for some time, as in the present case, and suggests that the circulating 5-hydroxytryptamine must have been in some way responsible.

Brain (1957) points out that a sudden fall of blood pressure from any cause is probably the commonest cause of syncope, and states that the most important fact about the regulation of the cerebral circulation is its peculiarly close dependence upon the systemic blood pressure, but quotes Schmidt (1950) as saying that whilst the cerebral circulation normally tends to follow passively upon changes in arterial pressure to a greater extent than is the case in most other organs, it probably has greater capacities for resisting or compensating for such states than has been suspected. As 5-hydroxytryptamine occurs normally in the brain (Woolley and Shaw, 1954), and as it has been shown (Taylor, Page and Corcoran, 1951) that in the dog a pressor substance which is probably 5-HT is released into the venous blood from the head when the cut end of the vagus nerve is stimulated electrically, the possibility arises that 5-HT is concerned in the normal regulation of the cerebral blood flow, perhaps being released as a result of reflex stimulation of the carotid sinus and aortic nerves by a fall in systemic blood pressure.

Summary

A report is made of a case of malignant carcinoid tumour with hepatic metastases, giving rise to the 5-HT syndrome of attacks of flushing of the face and neck, diarrhoea and vomiting, with the unusual feature of severe circulatory collapse. Full consciousness was retained in the presence of an unrecordable brachial blood pressure, indicating selective maintenance of the cerebral circulation, and the possible implications of this are briefly discussed.

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able in an operating theatre, is the optimum route of delivery for these patients, thereby avoiding altogether the possible rise of blood pressure in labour and delivery and lessening the risk of subsequent endo-aortitis. This is the view shared by Benham (1944), Bramwell (1953), and Rosenthal (1955). The latter writer comments that 6 out of the 11 cases of pregnancy and coarctation which terminated fatally died in labour or near term.

While advocating an elective Caesarean section for primigravidae, where the condition is met after a previous normal vaginal delivery, we suggest that a further vaginal delivery could be allowed when a short first stage of labour and a rapid normal second stage can confidently be expected. The first two case reports show this carried out in practice. The first had had two deliveries, there was no evidence to suggest any expected obstetric difficulty, and the second stage in fact lasted 10 minutes. The second patient gave a history of a difficult forceps delivery, there was some outlet contraction present, so a Caesarean section was decided on.

In addition to this proposed method of delivery, it is obvious that patients with coarctation must receive careful ante-natal care, periods of rest if cardiac symptoms arise, and antibiotic prophylaxis in the puerperium as advocated by MacLeod (1954).

Two of our cases developed pre-eclamptic toxaemia in the last trimester of their pregnancies. It is surprising that this added hazard has not been noted more frequently in view of the higher incidence of toxaemia that occurs in patients suffering from essential hypertension. If, as some authorities suggest, the hypertension of coarctation is a product of renal ischaemia, then these patients would be expected to be very liable to develop pre-eclamptic toxaemia. It is also of interest to note that in both these cases the coarctation had been resected.

Although resection during pregnancy has been described several times, Pritchard (1953) emphasized the risk to the foetus from prolonged anoxia and this is borne out by the history of Case 4, where abortion occurred 48 hours after operation.

Webbing of the neck is a characteristic feature of the syndrome of gonadal dysplasia described by Turner (1958) and Albright et al. (1942), and coarctation is sometimes found as an additional feature. Grumbach (1955) described 22 cases of gonadal dysplasia with 12 showing webbing and coarctation and found them all to be chromosomal males, which is another typical feature of this syndrome. Case 5 where webbing and coarctation were present and obviously not associated with gonadal dysplasia must therefore be of exceptional rarity.

Summary
The incidence and hazards of coarctation of the aorta associated with pregnancy are discussed. Five case reports are presented and the obstetric management described. The conclusion is drawn that, in general, these patients are best delivered by an elective Caesarean section.

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