HYPOGLYCAEMIA WITH WILMS' TUMOUR*

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Hypoglycaemia occurring in association with certain extrapancreatic tumours, mesodermal in type and mostly malignant, has become a well-established entity of organic hypoglycaemia. Conn and Seltzer (1955), in a review of spontaneous hypoglycaemia, added this group to the well-known causes of organic hypoglycaemia, namely, pancreatic, hepatic, anterior pituitary, adrenocortical and central nervous system lesions (Table).

TABLE
AETIOLOGICAL CLASSIFICATION OF SPONTANEOUS
HYPOGLYCAEMIA

(Abbreviated from Conn and Seltzer)

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- I. *Organic*: Recognizable anatomical lesion
- (1) Hyperinsulinism: (a) pancreatic islet-cell adenoma
(b) pancreatic islet-cell carcinoma
(c) generalized hypertrophy and hyperplasia of the islets of Langerhans
 - (2) Hepatic disease
 - (3) Anterior pituitary hypofunction
 - (4) Adrenocortical hypofunction
 - (5) Fibromas and sarcomas
 - (6) Central nervous system lesions: hypothalamus or brain-stem interference with the nervous control of blood sugar
- II. *Functional*: No recognizable anatomical lesion, explained on basis of unusual somatic function
- (1) Hyperinsulinism: imbalance of the autonomic nervous system
 - (2) Alimentary hyperinsulinism: rapid intestinal absorption
 - (3) Hyperinsulinism of infancy: Staub-Traugott phenomenon
 - (4) Idiopathic spontaneous hypoglycaemia of infancy
 - (5) Renal glycosuria: severe degrees of low renal threshold for glucose
 - (6) Lactation
 - (7) Severe continuous muscular work
- III. *Factitious*: Exogenous hyperinsulinism (surreptitious insulin administration)
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Although 32 cases only have been recorded up to June 1962 (de Coster, Payfa, Bellens, Conard and Bastenie, 1962), there is more awareness of the condition today, as evidenced by an increasing report of cases. Since Doege (1930) reported the first case and established subsequently the relation

of the tumour to hypoglycaemia, only six cases were described before 1954 (Seckel, 1939; Arkless, 1942; Hines, 1943; Staffieri, Cames and Cid, 1949; Skillern, McCormack, Hewlett and Crile, 1954). However, from 1955 to 1962, 25 more cases were added (our case is the 33rd). All these tumours, without exception, have been described in adults, and ours is the first to be recorded in a child. The purpose of this communication is to introduce this entity to paediatricians and to familiarize all those concerned with the main aspects of the disease.

Case Report

A 5-year-old boy was admitted to the University Children's Hospital, Mounira, on February 17, 1962, on account of a swelling in the abdomen of two weeks' duration. Unusual voracious appetite was noticed for two weeks before admission and the parents sought medical advice. They were told that the child had a mass in the abdomen, possibly an enlarged spleen, and were referred to the Children's Hospital. There was no pain in the abdomen, no urinary disturbances and no gastrointestinal upsets. However, the child had seemed to be off colour.

Examination revealed a quiet co-operative child, somewhat pale, with blood pressure 140/100 mm. Hg, and a normal temperature. Palpation revealed a mass in the left lumbar and hypochondrial regions, the size of a grapefruit, firm with a smooth surface, not tender and not moving with respiration. The descending colon could be rolled over it. The right kidney and liver were not palpable. The spleen was not enlarged. No other mass could be felt. The preliminary diagnosis was a left Wilms' tumour.

The following day, two hours after intravenous pyelography, the patient suddenly became unconscious. At first, this was thought to be momentary, but it persisted for six hours. No explanation could be given at the time, although some advanced the possibility of an allergic reaction to Uroselectan. However, 25% glucose, 50 ml., was given on an empirical basis, and to the great surprise of those attending the case, the child recovered.

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FIG. 1.—Patient unconscious during a hypoglycaemic attack.

FIG. 2.—Recovery after a 45-ml. injection of glucose, 25%.

Next day, the possibility of hypoglycaemia was suggested and that of allergy rejected. It was decided to fast the child to precipitate a hypoglycaemic attack. Next morning, the child was comatose. Examination during the crisis (Fig. 1) revealed a completely unconscious child with no response to pin prick and absent conjunctival

reflex; the pulse rate was 112 a minute; blood pressure 140/90 mm. Hg, temperature 37° C. There were no convulsions. The eyes were almost closed, the pupils constricted with no squint. The limbs were flaccid. Excessive perspiration was characteristic. A blood sample was taken for glucose determination. Intraven-

FIG. 3.—Glucose tolerance test curve; fasting level, 35 mg., peak at 90 mg. at one hour, then slow fall.

FIG. 4.—Intravenous pyelography showing normal right kidney function and hydronephrosis on the left side; poor visualization of the lower calyces.

ous glucose, 25%, was then administered. After 30 ml. the eyes were half open, and after 45 ml. the child opened his eyes completely, moved in bed and recovered consciousness (Fig. 2). The blood sugar during the episode turned out to be 27 mg./100 ml. Hypoglycaemia was thus confirmed. For further proof a glucose tolerance test was performed. It showed a low fasting level (35 mg.), a peak at one hour (90 mg.), then a slow fall (Fig. 3).

Excretory urography (Fig. 4) showed a good right kidney function. However, on the left side there was a big opaque shadow that had displaced the intestinal gas shadows to the right; the kidney showed a distorted pyelogram with dilated upper calyces, displaced pelvis, and poor visualization of the lower ones. The diagnosis of Wilms' tumour of the left kidney was confirmed. Other investigations showed: blood urea 23 mg./100 ml.; Hb 72%; white blood cells 11,000, polymorphs 59%, lymphocytes 39%, monocytes 2%. The urine showed traces of albumin, few pus cells, no casts and no *Bilharzia* ovae; 17-ketosteroids, 0.7 mg./24 hours; blood proteins, 6.5 g./100 ml.

While in hospital, the child complained of pain in the abdomen; he felt more comfortable on lying prone, and he stopped over-eating. He had another attack of hypoglycaemia relieved by intravenous glucose. For the few days he spent in hospital pending operation, there was sugar at the bed-side to avert any hypoglycaemic attack. We were faced now with the problem of a child having a Wilms' tumour and suffering from hypoglycaemia, which conformed to the typical Whipple's triad, namely, attacks of nervousness or gastro-intestinal disturbances occurring on fasting, associated with a low blood sugar (below 50 mg.) and relieved by administration of glucose. Pancreatic islet-cell tumour was considered a possibility, and it was decided that the pancreas should be explored during the operation for Wilms' tumour.

Operation. Intravenous glucose was given throughout the operation by drip, in addition to blood transfusion. A transperitoneal approach through an extensive left paramedian incision was performed. No fluid was detected in the peritoneal cavity. Exploration of the abdomen revealed normal liver and spleen, a normal right kidney, and no mass in the right adrenal gland and pelvis; there was a big firm tumour filling the left loin and hypochondrium. The descending colon was intimately adherent to it anteriorly and actually involved in the mass; it looked bluish in contrast to the rest of the colon. The spleen was also attached to the mass. So the question arose whether to consider the case inoperable and close and be satisfied with radiotherapy and chemotherapy, or attempt radical extensive surgery with its hazards. The descending colon was severed above and below the tumour, and continuity restored by end-to-end anastomosis. Adherent omentum was cut and left *in situ*. While dissecting medially to expose the renal vessels, the tail and distal part of the body of the pancreas were found infiltrated with the tumour; partial pancreatectomy was unavoidable. Many small vessels had to be ligated before

the distal pancreas could be freed from its bed. The tumour with the involved left kidney, the distal pancreas, the spleen and the descending colon were all removed in one mass. The aorta was carefully cleared of residual lymph nodes. The left suprarenal gland was not infiltrated, and so was left behind.

After the operation, the patient received hydrocortisone and glucose. Next day, the fasting blood sugar rose to 180 mg./100 ml. The blood pressure dropped to 105/80 mm. Hg. Unfortunately, a few days later, the wound showed infection and pus was drained. This retarded convalescence and the use of post-operative deep x-ray therapy. Cyclophosphamide ('endoxan') was given, as actinomycin D was not available. The child was then discharged and instructed to attend out-patients' department once a month for a regular check-up. He had no further attacks of hypoglycaemia, and since the operation he has been doing well with no more pain; the latest recorded fasting blood sugar was 92 mg./100 ml. No metastases have appeared in the chest so far.

Pathology. The specimen consists of the left kidney with a big tumour mass arising from its antero-lateral surface, the spleen, descending colon, tail and part of the body of the pancreas which is attached to the upper pole of the tumour (Fig. 5). It weighs 820 g. The cut section of the kidney and the tumour (Fig. 6) is oval, 17 × 10 cm., greyish white, homogeneous with small areas of necrosis, and without cystic formation. The tumour has totally destroyed the central zone of the kidney from which it probably arose, infiltrated the adjacent upper and lower zones and, in the main, has grown extrarenally. The descending colon is firmly adherent, and on opening it the posterior wall is extensively infiltrated. The distal part of the pancreas is also infiltrated by the tumour. The draining lymph nodes are enlarged, some of them 2 cm. diameter. There is no evidence of thrombi in the renal vein.

Microscopy. The tumour consists of sarcomatous tissue made in areas of oval or round cells, while in others spindle cells preponderate (Fig. 7). Gordon silver stain shows reticular fibres in between. In other areas, the neoplastic cells appear polygonal with pale staining cytoplasm and round or oval nuclei. No tubular structure could be identified. The tumour has infiltrated the kidney, the muscular coat of the descending colon and appears under the mucosa which is ulcerated in some areas. The pancreas is also infiltrated with tumour tissue, but the islets of Langerhans are normal, and there is no evidence of islet-cell tumour (Fig. 8).

In conclusion, the tumour is a Wilms' tumour that has invaded neighbouring organs. The pancreas, apart from direct infiltration, is otherwise normal in structure.

Discussion

Available data from reported cases of extra-pancreatic mesodermal neoplasms associated with hypoglycaemia demonstrate features that are peculiar

FIG. 5.—Specimen, posterior aspect, showing left kidney tumour, spleen, distal pancreas and descending colon.

to these tumours. They are characteristically bulky when hypoglycaemia sets in, and can thus be recognized clinically, in contrast to islet-cell tumours which are usually too small to be identified clinically, or even at operation (Monro, 1960). Many show degeneration, cavitation and cystic formation. They are commonly encountered in the retroperitoneal region of the abdomen, and less commonly in the

mediastinum in the thorax. Most of them show a spindle-cell type of structure or a variant of it. Where a tumour was clinically evident, its excision was followed unnecessarily by partial pancreatectomy when the tumour-hypoglycaemia relation was unrecognized. Where the tumour was in an inaccessible site, such as the diaphragm, and was undiagnosed before operation, exploration of the

FIG. 6.—Cut section of the tumour and kidney showing homogeneous appearance of the tumour.

FIG. 7.—Photomicrograph ($\times 196$) showing round or oval cells amongst which can be seen spindle cells.

abdomen and of the pancreas was negative and partial pancreatectomy was performed (Whitney and Heller, 1961). The patients failed to improve after operation, and months later the tumour became

evident. The patients were operated on again to extirpate tumour masses and consequently were cured of the hypoglycaemia.

In all cases, where the tumours were excised the

FIG. 8.—Photomicrograph ($\times 150$) showing sarcomatous cells infiltrating the pancreas which is otherwise normal.

hypoglycaemia disappeared. However, it returned when the tumour recurred (Porter and Frantz, 1956; Stauffer, Granville and Law, 1961). This observation led to these tumours being incriminated as the cause of hypoglycaemia. The explanation of the mechanism of hypoglycaemia aroused great interest: Seckel (1939) explained it in his case of a large fibroma of the right lobe of the liver as being due to pressure on the right splanchnic nerves and coeliac ganglion, thereby blocking the sympathetic impulses to the liver, which are known to mobilize glycogen. But although this may sound a possible explanation, it does not explain the hypoglycaemia associated with tumours situated away from the splanchnic nerves.

Skilern *et al.* (1954) thought that these neoplasms were atypical, functioning, islet-cell tumours of low-grade malignancy that masqueraded as sarcoma-like neoplasms. The presence of occasional round cells containing blue cytoplasmic granules, resembling pancreatic beta cells, in the tumour of one of their cases suggested to them that insulin was being produced by the tumour cells. However, insulin could not be extracted from the tumour tissue in either of their cases.

Hines (1943) postulated that the symptoms resulted from the direct action of a tumour-produced substance upon the pancreas, constantly stimulating insulin secretion. However, no hyperplasia or hypertrophy of the islets is demonstrable as would be expected. On the other hand, he postulated that the tumour released an insulin-like substance (insulinoid) that effectively lowered the blood sugar. He did not feel that the substance was insulin and thought that the tumour originated from fat cells: the substance liberated may have been an unusual fatty substance that might require a maximum of glucose to provide a hotter and more constant fire.

Scholz, Woolner and Priestley (1957) suggested that the tumour might liberate an insulinase inhibitor which has been demonstrated by Mirsky (1957) to compete with insulin for insulinase. Miller, Bolinger, Janigan, Crockett and Friesen (1959) in their two cases and four other previous cases, reported areas of cavitation, cystic degeneration and necrosis in the tumour. The association of the necrotic cystic areas, and the development of symptoms only after the tumour has assumed large proportions, suggests that a hypoglycaemic-producing substance with an action similar to insulin (or insulinase inhibitor) may be a breakdown product of tumour degeneration. Schonfeld, Babbott and Gundersen (1961) believed that in their case of hepatoma of the liver the tumour itself metabolized glucose in amounts greater than normal.

Some authors have estimated the plasma insulin activity as well as the tumour insulin activity. August and Hiatt (1958) were the first to demonstrate, in their tumour, insulin activity three times that found in the pancreas of a normal subject, using the rat-diaphragm method of Vallance-Owen and Hurlock (1954). Hayes, Spurr, Felts and Miller (1961) did an extensive metabolic study on their case. They found that in the oral and intravenous glucose tolerance curves, there was failure of secondary rise after the blood sugar reached its lowest level, and this was described as 'hypoglycaemia irresponsiveness'. They also showed that the free fatty acids in the blood were in the high normal range. In the event of hyperinsulinism, it is expected that these levels will fall in proportion to the degree of hyperinsulinism present. The inorganic phosphorus level was estimated as an index of peripheral utilization of glucose. The absence of a fall greater than 10% in the level of inorganic phosphorus was taken to indicate a diversion of glucose from the periphery. Probably, the tumour utilized excessive amounts of glucose, thus shunting it away from the periphery. The level of circulating lactic acid was within normal limits. An increase in lactic acid level would indicate a high level of glycolysis, an inefficient liver, or both.

Unfortunately, in our case, as occurred with previous authors, we did not fully appreciate the hypoglycaemia-tumour relation, and so no insulin bio-assays of the plasma were done. It was only a few days after the resection of the tumour, with the complete cessation of hypoglycaemia together with the absence of an islet-cell tumour in the pancreas, that the tumour-hypoglycaemia relation was established. This was confirmed by finding other recorded cases. The few who were aware of the relation performed the bio-assay. It is certainly desirable, whenever such cases are encountered, to perform a bio-assay and a full metabolic study, so that the nature of the hypoglycaemic agent may be clarified (Nesbitt, Boswell, DeJesus-Gonzales and Sarkisian, 1958).

In our case, Wilms' tumour was associated with hypoglycaemia; such an association has not been recorded before. It was a highly malignant sarcoma, and although we have operated on 41 cases of Wilms' tumour during the past 10 years (1952-61), this one infiltrating the colon, pancreas and retroperitoneal structures seems to be the most malignant. In the whole reported series of tumours with hypoglycaemia, only one case has been associated with a renal tumour (Scholz *et al.*, 1957). This occurred in a 47-year-old man diagnosed, pre-operatively, as malignant islet-cell tumour of the pancreas and

subsequently proved to be a well-differentiated fibrosarcoma situated beneath the renal capsule and compressing the renal parenchyma.

In conclusion, it is not surprising to find the hypoglycaemia of sarcomata, when described in childhood, to be associated with Wilms' tumour, as the latter has always been known to be the commonest abdominal malignant tumour in childhood.

Summary

Hypoglycaemia associated with certain malignant tumours, mesodermal in type, is described. All occurred in adults. This case of Wilms' tumour is the first to be reported in the paediatric age-group.

With extirpation of the tumour, the hypoglycaemia subsides to return with recurrence of the tumour.

Different explanations of the hypoglycaemia are discussed, and the desirability of performing insulin bio-assays of the tumour and plasma and a metabolic study is emphasized, as well as the importance of being aware of the hypoglycaemia-tumour relation in order to avoid unnecessary pancreatic surgery.

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