Fulminating Diabetes with Lymphocytic Thyroiditis

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Recorded observations suggest strongly but not conclusively that auto-immunity is a factor in the pathogenesis of at least some forms of juvenile diabetes mellitus. This view is based on the occasional association of juvenile diabetes with Hashimoto's disease, which is a well-known example of auto-immunity, the presence of thyroid antibodies in some cases of diabetes, and the pathohistological features of the lesions in juvenile diabetes.

The problem of non-thyroid manifestations of auto-immunity in cases of Hashimoto's disease seems to be as yet unresolved. Blizzard, Chandler, Kyle, and Hung (1962) were so impressed by the frequency of associated endocrine involvement, e.g. of the adrenal, pituitary, and parathyroid, in cases of Hashimoto's disease, as to suggest that patients with one type of auto-immune endocrine disease are also liable to have another. On the other hand, though 11 of 74 cases of chronic thyroiditis in a post-mortem series surveyed by Masi, Hartmann, Hahn, Abbey, and Shulman (1965) suffered from diabetes mellitus, the latter was also present in 8 patients of their corresponding control series without thyroiditis. That auto-immune disorders may often be associated with thyroiditis can be seen from the series of Becker, Titus, Woolner, and McConahey (1965) who found that 36 of 153 cases of thyroiditis also suffered from such disorders as rheumatoid arthritis, pernicious anaemia, myasthenia gravis, thrombocytopenic purpura, Addison's disease, and glomerulonephritis. The incidence of focal thyroiditis in post-mortem sections of 724 thyroids was studied by Williams and Doniach (1962). They confirmed the correlation of Addison's disease and of panhypopituitarism with a raised incidence of thyroid involvement. The incidence of such involvement in the diabetics in their series was, however, not significantly higher than in controls.

The above studies were mostly on adults. The position seems to be more clear cut in children and adolescents. Thyroid antibodies were found in 13 of 58 diabetic children (22%) by Landing, Pettit,

Wiens, Knowles, and Guest (1963). This compared with 2 of 178 (1%) in non-diabetic children. The results of a study in Sweden and London of 35 cases of juvenile lymphocytic thyroiditis have been published by Nilsson and Doniach (1964). Two of the patients had diabetes mellitus diagnosed before the onset of the thyroid disease.

Evidence in favour of auto-immunity as a factor in juvenile diabetes is perhaps stronger on the histological plane. The typical lesion of thyroiditis is lymphocytic infiltration of the gland, and somewhat similar changes have been observed in some pancreases of diabetic infants and children. Of five pancreases of diabetic infants dying within the first year of life, four showed lymphocytic islet and interstitial infiltration (Lawrence and McCance, 1931). Warren and Le Compte (1952) report that lymphocytic infiltration of the islets was present in 11 of 811 pancreases of diabetic patients; of these 11, 3 were under 10 years at the time of death, and 8 were under 30. The authors state that in cases showing lymphocytic infiltration of the islets the disease tends to be particularly severe. Lymphocytic infiltration of the pancreas was observed in 4 of 74 cases of Hashimoto's disease by Masi *et al.* (1965). Adequate sections of the thyroid gland were available from 11 apparently euthyroid diabetic children studied by Landing *et al.* (1963). Two of these showed evidence of chronic thyroiditis. The state of the pancreases in this series was not described. Experimental work is also suggestive of auto-immunity. Insulin injected into rabbits results in the production of antibodies that bind and inactivate exogenous and endogenous insulin (Toreson, Lee, and Grodsky, 1966). Most of their experimental animals showed permanent or periodic diabetes. Degenerative changes and lymphocytic infiltration were present in the islets of these animals.

We have had an opportunity to study the clinical and pathological findings in a child suffering simultaneously from diabetes mellitus, focal lymphocytic thyroiditis, and transient haemoglobinuria. The case seems to us to have theoretical and practical interest, and the findings are presented below.

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Case Report

A girl aged 8 years was admitted to hospital in October 1966. She had been born after a normal pregnancy and confinement, birthweight 4.1 kg. Her parents and 14-year-old twin brother and sister are well. The child developed normally, the only noteworthy illnesses being mumps, measles, and rubella. During her 8th year, however, she is said to have suffered twice from tonsillitis. She had been treated at home with oral penicillin for a third attack of tonsillitis two weeks before admission, following which she was noted to be drinking excessively. During the week before admission she had lost weight, developed polyuria, and had been vomiting.

On admission she was conscious and alert with signs of marked dehydration and a temperature of 37° C. Her throat was injected, but physical examination revealed no other abnormality.

Laboratory investigations on admission revealed: Hb 12.7 g./100 ml., WBC 18,400 c.mm., with neutrophils 86%, lymphocytes 11%, monocytes 3%. RBC's showed some polychromasia. Platelets 175,000 c.mm. Direct Coombs test negative. ESR (modified Westergren) 2 mm. in first hour. Blood sugar 615 mg./100 ml. Blood urea 34 mg./100 ml.; serum bilirubin 1.6 mg./100 ml.; serum sodium 128 mEq/l.; serum potassium 5.5 mEq/l.; serum chloride 98 mEq/l. CO₂ combining power, less than 5.0 mEq/l. The urine contained sugar, ketones, and a trace of protein.

The patient was given soluble insulin 30 units, intramuscularly, and fluids, 0.18% saline with added sodium bicarbonate followed by 4.3% dextrose and 0.18% saline, with 0.5 g. potassium chloride/500 ml. fluid, intravenously. Ampicillin 250 mg. was given 6-hourly intramuscularly.

Four hours after admission she passed a clear specimen of red urine. No red cells were found on microscopical examination of the deposit; absorption bands of oxyhaemoglobin were detected spectroscopically. Six hours later her blood sugar had been reduced to 220 mg./100 ml. Blood urea 27 mg./100 ml., serum bilirubin 2.7 mg./100 ml., serum amylase 120 Somogyi units, SGOT 20 Sigma-Frankel units, SGPT less than 5 Sigma-Frankel units, serum sodium 126 mEq/l., serum potassium 3.5 mEq/l., serum chloride 100 mEq/l., CO₂ combining power 8.5 mEq/l. No absorption bands of haemoglobin were found on spectroscopic examination of the serum at this time.

Although previously alert, she became progressively drowsy and two and a half hours later was comatose. Two hours later she developed neck rigidity and her plantar responses were found to be extensor. A convulsion then occurred and was followed by apnoea. She was given calcium gluconate 500 mg., hydrocortisone sodium succinate 100 mg., and nikethamide 1 ml. intravenously; no improvement in her condition followed and she was intubated and ventilated by a respirator. Lumbar puncture yielded normal CSF under normal pressure. She was given a further 100 mg. hydrocortisone sodium succinate intravenously, and her blood sugar levels during the day fluctuated between 216 mg./100 ml. and 136 mg./100 ml., controlled with soluble

insulin. She remained comatose and died within 36 hours of admission.

Blood culture was negative after 17 days of incubation.

Necropsy. The body (weight 19 kg., height 125 cm.) presented no external abnormality. Double ureters were present on the right side. The brain showed marked flattening of the cerebral gyri and uncinate grooving indicative of brain swelling or oedema. The adrenals were somewhat small.

Weights of the main organs were as follows: brain 1380 g.; kidneys 63 g. and 58 g.; adrenals 4.0 g. and 4.8 g.; thymus 12 g.; thyroid 14 g.; lungs 139 g. and 108 g.; pancreas 25 g.; spleen 63 g.; pituitary 0.2 g.; heart 90 g.

Microbiology. No pathogenic bacteria were grown from post-mortem tissues. No viruses were isolated in tissue culture from the cervical cord, a cervical lymph node, or faeces (Dr. H. Stern).

Serology. No serological tests were done on the patient's serum. The sera of the parents and the twin sibs were, however, tested after the patient's death against thyroid, stomach, and kidney (Dr. I. M. Roitt). Positive reactions were obtained with the father's serum, which was positive for antinuclear factor (titre 1/10), and the mother's serum, which contained weakly positive antibodies to the thyroid cytoplasmic antigen (immunofluorescent test).

Histological findings. The following tissues were embedded in paraffin and examined after staining with haematoxylin and eosin, haematoxylin and van Gieson: skeletal muscle, adrenals, pituitary, heart, kidneys, spleen, liver, ovary, lungs, thymus, bone-marrow, thyroid, bladder, pancreas, and all representative levels of the central nervous system. In addition, special stains were used for sections of the thyroid, pancreas, and liver, and some of these are mentioned in the description below.

The *thyroid* showed generalized focal lymphocytic infiltration (Fig. 1). The cellular exudate consisted exclusively of lymphocytes, and germinal centres had formed in some areas. The density of the exudate varied considerably, some small areas being free from it. Elsewhere the thyroid follicles were either replaced by the exudate or showed marked reduction in size and disappearance of the colloid. The amount of collagenous fibrous tissue was increased.

In the *pancreas* many islets of Langerhans showed lymphocytic infiltration and degenerative change (Fig. 2). In those least affected, lymphocytes were usually present around the periphery of the islet; elsewhere the distribution of the exudate varied considerably. No lymphocytes were present in the exocrine tissue of the pancreas. In addition to the lymphocytic infiltration many islets showed fading and necrosis of the cells. No surviving islet cells could be found in the most affected formations. In some islets there also appeared to be clumping of the cells. Attempts to establish the identity of the surviving

FIG. 1.—Lymphocytic infiltration of the thyroid. Early follicle formation to the right of the centre. (H. and E. $\times 160$.)

cells by the Gomori methods of staining were unsuccessful. Many of the cells stained red by the chrome alum haematoxylin method, and thus appeared to be α cells, but some of these also contained purple granules when stained by the aldehyde fuchsin method, thus resembling β cells.

The liver showed considerable fatty change and

marked accumulation of glycogen, especially in the centrilobular areas. The adrenal cortices were perhaps marginally small but showed no other abnormality. A few scattered lymphocytes were present in the adrenal medulla. The lungs showed a few small areas of lobular collapse. The red pulp of the spleen contained an excess of polymorphs. The pituitary, thymus, bone-

FIG. 2.—Necrosis and lymphocytic infiltration of an islet of Langerhans. (H. and E. $\times 400$.)

FIG. 3.—Acute necrosis of the cerebellar granular layer. (H. and E. $\times 160$.)

marrow and other somatic organs appeared normal. Slight lymphocytic infiltration was present beneath the mucosa in the pelves and calyces of the *kidney* and the *bladder*.

The most conspicuous neural changes were observed in the cerebellum. This showed marked necrosis of the granular layer (Fig. 3). Many of the cells had faded completely and the tissue presented a loose reticular pattern. Other cells were clumped in small groups. Some Purkinje cells had also disappeared, but this layer was nevertheless relatively well preserved. The molecular layer and the white matter of the cerebellum showed no abnormality. Elsewhere the grey matter showed unevenness of staining, some neuronal shrinkage, and 'ischaemic change'. Oedematous vacuolation was present around many neurones in the cortex and sub-cortical formations, and the matrix of the cortex also showed very small cavities measuring up to 1–3 μ . There seemed to be no accentuation of the degree of change in any particular formation other than the cerebellum.

Discussion

During life the case was diagnosed and treated as one of diabetes mellitus. The haemoglobinuria remained unexplained. Thyroiditis was not suspected. The pathological findings indicate, however, that the thyroiditis had been present for a considerable time. It is known that thyroiditis of the Hashimoto type may remain symptomless and produce little goitre (Nilsson and Doniach, 1964), and this may have happened in the present case. On the other hand, the localization of the discomfort by the child may have been imperfect and the

thyroiditis may have been mistaken for 'tonsillitis'. In view of the previously reported association of diabetes mellitus and thyroiditis it seems worth while to bear in mind the possibility of thyroiditis and hypothyroidism during the management of diabetes in children.

An auto-immune disease was not suggested in this case while the patient was alive, and because of the rapid course investigations did not include testing the patient's serum for antibodies. The histological findings are, however so characteristic of auto-immunity as to put the pathogenesis beyond reasonable doubt. This is in conformity with the presence of the antinuclear factor in the serum of the patient's father, and of the antibodies to the thyroid cytoplasmic antigen in the mother's serum. It has been shown by Doniach, Nilsson, and Roitt (1965) that such a correlation is present in many families of juvenile cases of thyroiditis.

Atrophy of the granular cerebellar layer is one of the recognized changes in diabetic neuropathy and has been seen by us in several other cases of juvenile diabetes. It is, however, usually chronic, and the onset of the acute necrosis in the present case is not fully explained.

Summary

A girl aged 8 suddenly developed an acute diabetic state and coma with associated transient haemoglobinuria. She died in spite of treatment directed at the diabetes. Post-mortem findings

showed the presence of focal lymphocytic thyroiditis and lymphocytic infiltration of the islets of Langerhans. The cerebellum showed acute necrosis of the granular layer.

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