Mortality in juvenile diabetes mellitus over 25 years

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Smith, C. S., and Hudson, F. P. (1976). Archives of Disease in Childhood, 51, 297. Mortality in juvenile diabetes mellitus over 25 years. Deaths over the past 25 years associated with diabetes mellitus under the age of 15 years are reviewed. Information is derived from the Registrar General's figures for England and Wales and from the records of a large paediatric diabetic unit.

In the preinsulin era diabetic ketoacidosis was a condition with a high mortality (Joslin and Wilson, 1950), but with modern treatment a dramatic fall in the number of deaths has occurred. Several authors (Harwood, 1951; Greenaway and Read, 1958) have quoted mortality figures varying from 2 to 15%, but most series cover the whole age range of diabetes mellitus.

In the juvenile age group it is probable that the mechanism of death will be concerned with the acute metabolic process, and will not be influenced by the long-term complications of the disease. From published reports and the Registrar General's annual reports it is not possible to ascertain the exact cause of death associated with diabetes in children nor, and we regard this as of considerable importance, can one determine how many children died at the onset of the disease and how many during the course of treatment.

Materials

The Registrar General's figures for England and Wales over the past 25 years have been studied, but they may not be completely accurate. There is no indication of the incidence of juvenile diabetes mellitus nor of the mechanism of individual deaths.

Alder Hey Children's Hospital has a large paediatric diabetic population comprising the majority of the juvenile diabetic patients from the Merseyside district, but also including some problem diabetic children from surrounding areas. 50 patients were in regular attendance in 1950 and the number had increased to 118 by 1974. The average yearly increment in the years 1950–59 was 16 new patients, 1960–69 12 new patients, and 1970–74 16 new patients. The majority of the children come under the care of one of us (F.P.H.). Hospital records indicate 10 deaths associated with juvenile diabetes mellitus over the past 25 years which are evenly spread until 1968. After that there was a death-free period of 5 years until 1974 when a 10-year-old girl died in our unit with diabetic ketoacidosis.

Results

It can be seen from Fig. 1, that the total mortality under the age of 15 years fell slightly over the early part of the 25-year period. Since then this trend has become less obvious and the total number of deaths per year associated with juvenile diabetes mellitus is still notable and disturbing. In contrast, the mortality associated with diabetes mellitus in adults has increased continually over the 25-year period.

At this hospital the mean age at death of the 10 patients was 8 years. 8 of the 10 deaths occurred in children with previously undiagnosed diabetes mellitus, 6 of these within 24 hours of admission to hospital. All the deaths except one occurred in the months September to March. Associated

Fig. 1.—Mortality in juvenile diabetes mellitus from the Registrar General’s Statistical Review for England and Wales (1948–72).

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factors were respiratory infection in 4 patients, hypokalaemia 2, inhalation of gastric contents 2, and one death complicated by hyperosmolality and probable diabetes insipidus (Case 1). This latter problem is now described in more detail and is followed by brief details of the other deaths.

Case 1. A female who died in 1974 aged 10 years. Problems with recurrent ketoacidosis and nonacceptance of the restraints of a diabetic life. Her insulin requirements before the terminal illness had risen to 100 units/day as compared with 12 units/day at diagnosis of diabetes 22 months earlier. In her final episode of diabetic ketoacidosis she improved with standard treatment over the first 24 hours. A significant metabolic acidosis persisted and was treated with intermittent intravenous sodium bicarbonate solution in quantities calculated to half-correct her estimated deficit.

Over the next 12 hours she relapsed biochemically and became comatose with a gradual increase in serum Na to 167 mEq/l and in serum osmolality to 350 mOsm/l. These biochemical changes are shown in Fig. 2. In addition, she had profound polyuria—up to 800 ml/h of hypo-osmolar urine—which was initially responsive to aqueous pitressin, suggesting concomitant diabetes insipidus. She remained unconscious with severe hyperosmolality until death 84 hours after admission.

One kidney only was available for post-mortem study which showed nonspecific changes of swelling and vacuolation of renal tubular cells, with no evidence of acute cortical necrosis or diabetic-related renal pathology.

![Graph](image)

**Fig. 2.—Case 1. Biochemical values and insulin dosage during terminal illness.**

Case 2. A male died in 1950 aged 11 years. Symptoms were suggestive of diabetes mellitus, but presented surgically with an 'acute abdomen'. Laparotomy showed only acute gastric dilation and correct diagnosis was not made until the following day. Blood glucose by this time was >1000 mg/100ml and he died on that day despite treatment for severe diabetic ketoacidosis.

Case 3. A female died in 1951 aged 17 months. Presented with pneumonia and diabetic ketoacidosis, and responded satisfactorily to initial treatment. Hypoglycaemia provoked a sudden convulsion which was terminated by intravenous glucose. 12 hours after admission she collapsed suddenly and died. Necropsy was not performed.

Case 4. A female died in 1951 aged 5 years. A previous history of 'cyclical vomiting' caused delay in referral to hospital when vomiting developed due to diabetic ketoacidosis. Blood glucose on admission was 1400 mg/100ml and she died 3 hours after admission despite treatment. Necropsy showed evidence of inhalation of gastric contents.

Case 5. A female died in 1955 aged 8 years. Presented with diabetic ketoacidosis after a 3-week history of classical symptoms. She received 60 units soluble insulin initially and intravenous molar lactate solution. This produced clinical improvement, but she died suddenly 6 hours after admission. Her serum K before death was 1·5 mEq/l, but additional K was delayed and she received a further 25 units soluble insulin. Necropsy showed inhalation of gastric contents, extensive aortic atheroma, and some adrenal calcification.

Case 6. A female died in 1957 aged 2 years. Records were incomplete, but she died within 24 hours of admission with severe dehydration due to diabetic ketoacidosis. Extensive cerebral venous thromboses were evident at necropsy.

Case 7. A male died in 1961 aged 9 years. Was a known diabetic for 6 years who required residential accommodation because of domestic instability. He was admitted for reassessment of diabetic control and this was improved by using protamine zinc insulin. However, he developed ketoacidosis for no apparent reason and with intravenous rehydration his condition improved. He remained severely acidotic and died in coma several days later. No necropsy was carried out.

Case 8. A female died in 1966 aged 9 years. Was admitted in coma and dehydrated due to a respiratory infection aggravating diabetic ketoacidosis. She required intermittent positive pressure ventilation and made no response to treatment. Necropsy examination showed multiple staphylococcal lung abscesses.

Case 9. A female died in 1967 aged 13 years. After a 4-day history of cough and abdominal pain was admitted in coma with a blood glucose of 1040 mg/100ml.
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She died within 45 minutes of admission and necropsy was not performed.

Case 10. A female died in 1968 aged 13 years. There was a 6-week history of classical symptoms followed by a respiratory infection. She was admitted in diabetic coma with hypokalaemia (3.2 mEq/l). One cardiac arrest was successfully overcome, but was followed by ventricular fibrillation, hypotension, and death. Her hypokalaemia became more profound (serum K 1.6 mEq/l) despite large K supplements. Necropsy showed a severe bronchopneumonia.

Discussion

In patients dying from diabetes mellitus under 15 years of age the profound metabolic disturbance is the cause of death rather than the long-term vascular-renal complications. Such complications are rarely seen before diabetes has been present for over 10 years (White, 1960). The Annual Report of the Registrar General (1948—72) indicates a notable mortality, even in recent years with improved management of diabetic ketoacidosis. However, these figures may be inaccurate or incomplete and it is hoped that much more valuable information with regard to diabetic mortality will be provided by the survey organized by Dr. T. D. R. Hockaday (Radcliffe Infirmary, Oxford) presently in progress.

The classical symptoms of diabetes mellitus are polydipsia, polyuria, and weight loss. The first two of these symptoms are present in all children at the onset of clinical diabetes. They may have been present for a few days only, often for 2 or 3 weeks, and rarely for 3 months or more. Clinical suspicion of the diagnosis is easily confirmed by the finding of glycosuria and usually acetonuria. A glucose tolerance test is seldom indicated. It is important that prompt referral, by telephone, to a paediatric unit follows diagnosis. This is essential as incipient ketoacidosis can progress to coma within several hours if the appropriate treatment is delayed.

It is probable that the mechanisms of death in cases of juvenile diabetes at this hospital are representative of the national situation over the 25-year period. The management of ketoacidosis in this hospital has followed conventional methods with intermittent soluble insulin, intravenous fluid replacement with normal saline initially, intravenous potassium supplements, and either molar lactate or sodium bicarbonate to partially correct the metabolic acidosis. Known diabetics are encouraged to telephone a member of the diabetic team for advice or to come to the ward promptly if unwell or urine tests show excessive glycosuria or acetonuria.

In 8 of the 10 deaths the presenting feature was as severe metabolic disturbance due to ketoacidosis in a previously undiagnosed diabetic. Only 2 deaths occurred in children known to have diabetes mellitus and receiving treatment. In 5 of the 10 deaths critical analysis would suggest one or more preventable factors. In Case 2, for instance, an appreciation of the 'acute abdomen' presentation of diabetic ketoacidosis would have ensured earlier nonoperative treatment. Case 3 illustrates the sensitivity of small children to insulin and the ease with which hypoglycaemia can be produced. In recent years it has become apparent that the use of insulin and alkali therapy quickly aggravates potential hypokalaemia. Potassium replacement therapy is now advised early rather than later as was at one time the recommended practice. Case 5 and 10 had hypokalaemia of a significant degree and earlier replacement of potassium might have been life saving. In Cases 4 and 5 evidence was found at necropsy of inhalation of gastric contents which might have been prevented by gastric lavage and suction. Case 7 was a boy with diabetes mellitus of 6 years' duration who developed ketoacidosis and coma over a few hours while in hospital. The clinical picture and blood glucose improved with treatment but he remained acidic, and died in deep coma. This sequence of events is reminiscent of 3 deaths in adolescent diabetics described by Fitzgerald, O'Sullivan, and Malins (1961) who at necropsy showed evidence of cerebral oedema and necrosis.

Nonacceptance of a chronic condition is not infrequently seen in paediatric diabetic practice and is well illustrated by Case 1. The pattern of her final illness was again similar to that described by Fitzgerald et al. (1961). One of their patients had coexisting diabetes mellitus and insipidus. In our patient the brain was not available for necropsy examination, but Fitzgerald found massive destruction of midbrain and hypothalamus in their patient. Similarly, Taubin and Matz (1968) described a young female with the combination of diabetes mellitus and insipidus, who died with cerebral oedema and neuronal loss and anoxic hypothalamic changes on histological examination. The only histology available in our patient was from the kidney. The nonspecific changes of congestion and tubular cell vacuolation were similar to those described by Taubin and Matz (1968). These changes may be related to hyperosmolality as red blood cells in similar conditions have shown evidence of damage and vacuole formation (Kim, Borges, and Holliday, 1962). It has also been shown that the ability of peripheral cells to metabolize glucose is impaired in hyperosmolar states (Stevenson and
Bowyer, 1970). The apparent resistance to insulin action in our patient during her terminal illness could be partially explained by this factor in addition to ketoadiposis and dehydration.

The use of intravenous alkali therapy in the management of diabetic ketoacidosis has many advocates (Kuzemko, Fielding, and Hudson, 1969) but it is not deemed necessary by many units, including the Joslin Clinic, Boston, Mass. (Young and Bradley, 1967). Its use should be restricted to severely acidoctic patients and the amount of sodium bicarbonate administered should only be sufficient to half-correct the estimated deficit. In Case 1, large amounts of sodium, both as alkali to correct persisting severe acidosis and as sodium-containing fluids to combat dehydration, were administered. This sodium load was aggravated by profound polyuria in which excessive amounts of low solute fluid were lost.

The cerebrospinal fluid in this patient was under increased pressure and had a glucose content of 200 mg/100ml when the blood glucose was 500 mg/100ml. This indicates a delay in equilibrium between blood and cerebrospinal fluid. The opposite situation is described in similar patients reported by Hayes and Woods (1968) and Young and Bradley (1967). In addition the CSF pH was 7-57 when the blood pH was 7-25. This finding is at variance with the work of Posner, Swanson, and Plum (1965) who showed that the rapid correction of blood pH with sodium bicarbonate lowered the pH of the CSF.

Our patient had a clinical course compatible with cerebral oedema and damage probably arising from many factors including hyperosmolarity, ketoacidosis, and dehydration. One can only speculate on the amount, if any, of permanent cell damage resulting from the frequent episodes of diabetic ketoacidosis before the severe metabolic upset of her final illness.

While deaths from overwhelming infection and advanced diabetic complications may often be inevitable, this does not apply to death from otherwise uncomplicated diabetic ketoacidosis. In this article we have examined critically the deaths that occurred in one children’s hospital over a period of 25 years. Delay in diagnosis before, and in one case after, admission to hospital have played a part. More skilful management of the metabolic disturbance may come from the use of smaller doses of insulin given by intramuscular (Moseley, 1975) or intravenous (Page et al., 1974) routes.

REFERENCES


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