Conclusion

A careful social history may be particularly relevant in high gastrointestinal bleeding or perforation in the early newborn period. Conversely, such pregnancies should be regarded as particularly at risk and managed accordingly.

References

- Bird, C. E., Limper, M. A., and Mayer, J. M. (1941). Surgery in peptic ulceration of stomach and duodenum in infants and children. *Annals of Surgery*, **114**, 526–542.
- Dodge, J. A. (1970). Production of duodenal ulcers and hypertrophic pyloric stenosis by administration of pentagastrin to pregnant and newborn dogs. *Nature*, **225**, 284–285.
- Dodge, J. A. (1972). Psychosomatic aspects of infantile pyloric stenosis. *Journal of Psychosomatic Research*, **16**, 1–5.
- Karim, A. A., Morrison, J. E., and Parks, T. G. (1974). The role of pentagastrin in the production of canine hypertrophic pyloric stenosis and pyloroduodenal ulceration (abstract). *British Journal of Surgery*, **61**, 327.
- Revill, S. I., and Dodge, J. A. (1978). Psychological determinants of infantile pyloric stenosis. *Archives of Disease in Childhood*, **53**, 66–68.
- Rose, G. (1978). Aetiology and prevention. In *Medicine*, third series, part 1, pp. 5–6. Medical Education (International): Oxford.
- Smith, C. W., Jr (1975). Massive haemorrhage from multiple gastric ulcers in the newborn. A case report—with recent literature review. *North Carolina Medical Journal*, **36**, 97–99.

Correspondence to Dr R. J. Pugh, Department of Paediatrics, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ.

Hepatomegaly due to self-induced hyperinsulinism

JACK ASHEROV, MARC MIMOUNI, ITZHAK VARSANO, ERNESTO LUBIN, AND ZVI LARON

Institute of Paediatric and Adolescent Endocrinology, and Department of Nuclear Medicine, Beilinson Medical Centre, Petah Tikva, and the Sackler School of Medicine, Tel Aviv University, Israel

SUMMARY Repeated hypoglycaemic attacks, associated with transient hepatomegaly, in a 12-year-old insulin-dependent diabetic girl continued despite reduction in dose and, later, complete discontinuance of insulin. The attacks ceased while she was in hospital, necessitating reinstitution of insulin. The hepatomegaly resolved when surreptitious additional insulin injections were discovered and stopped. Hepatomegaly in diabetics should arouse suspicion of over dosage with insulin.

Hepatomegaly associated with diabetic hypoglycaemia was well known before long-acting insulin became available (Madison, 1969), but it has seldom been encountered recently (Rosenbloom and Giordano, 1977). We present a 12-year-old insulin-dependent diabetic with transient hepatomegaly associated with hypoglycaemia induced by surreptitious additional insulin injections, and discuss the role of over dosage with insulin in inducing hepatomegaly.

Case report

We have followed-up a 12-year-old girl since age 5 when insulin-dependent diabetes was diagnosed and treatment initiated. For 7 years control was good, but then frequent hypoglycaemic attacks of moderate severity were reported. The hypoglycaemic attacks persisted despite reduction in insulin dose and, later,

its complete discontinuance. Marked hepatomegaly was noted, and the girl was admitted for investigation.

She was then a lean, normotensive, healthy looking child with a firm, tender liver palpable 12 cm below the costal margin. SGOT 138 IU/ml (normal <40), LDH 156 IU/ml (normal <235), alkaline phosphatase 181 IU/ml (normal for age), acid phosphatase 1.5 U/ml (normal 0–1), bromosulphalein retention 2.4% after 45 min, serum ammonia 57 µg/100 ml (normal <85), antitrypsin 88 mg/100 ml (0.88 g/l) α-fetoprotein negative; normal bilirubin, electrolytes, and copper ceruloplasmin. Australian antigen tests, endocrinological studies including evaluation of pituitary and adrenal, and haematological study, including bone marrow aspiration, were all normal. Scan showed diffuse liver enlargement and a normal spleen (Fig. 1a).

After 3 days without treatment, the fasting serum insulin was 5.2 µU/ml. Because of hyperglycaemia (up to 405 mg/dl) and glycosuria (up to 4%), the insulin was restarted. The hypoglycaemic attacks then ceased, the liver size decreased to 6 cm below the costal margin, and she was discharged.

After 5 months of good control in which only the edge of the liver remained palpable (Fig. 1b) the hypoglycaemia and hepatomegaly recurred. Because of the history and laboratory findings, we suspected overinsulinism. The mother then discovered that the girl surreptitiously injected additional insulin, probably to attract notice by provoking hypoglycaemic spells.

Figure Liver scan. (a) Diffuse liver enlargement during overinsulinism; (b) Decreased liver size after adjustment of insulin dose.

We insisted that the extra insulin injections be stopped and referred the girl to a psychologist. The hypoglycaemic episodes then disappeared and the hepatomegaly resolved within a few weeks.

Discussion

After excluding diseases associated with hepatomegaly, the diagnosis lay between uncontrolled diabetes and over dosage with insulin. The long periods of good control and disappearance of hypoglycaemia during observation in hospital favoured the latter.

Rosenbloom and Giordano (1977) reviewing overtreatment in diabetic children noted findings similar to those of our patient. Hepatomegaly associated with protracted hypoglycaemia was noted before the availability of long-acting insulin, mainly among poorly controlled juvenile diabetics treated with daily, multiple injections of regular insulin (Mandell and Berenberg, 1974). The hepatomegaly of hyperinsulinism is thought to be secondary to accumulation of glycogen in the liver by inhibition of cyclic-AMP synthesis (Bishop *et al.*, 1965; Mortimore *et al.*,

1967; Davidson and Berliner, 1974; Dershewitz *et al.*, 1976). Insulin is known to affect hepatic glucose metabolism directly (Madison, 1969) by increasing the uptake and decreasing the output (Steele *et al.*, 1965). Liver glucose output is largely determined by opposing effects of insulin and glucagon (Jefferson *et al.*, 1968). Glucagon increases the hepatic cyclic-AMP, thus stimulating glycogenolysis and gluconeogenesis (Robison *et al.*, 1971). Insulin opposes this effect by inhibiting the synthesis and increasing the degradation of cyclic-AMP (Jefferson *et al.*, 1968), thus leading to increased glycogen storage.

The excessive insulin taken by our patient undoubtedly disturbed the balance between insulin and glucagon, leading to increased glycogen storage in the liver which presumably was responsible for the hepatomegaly. Stopping the insulin overdose, enabled the glucagon to increase the synthesis of cyclic-AMP, thus inducing glycogenolysis and resolution of the hepatomegaly.

References

- Bishop, J. S., Steele, R., Altszuler, N., Dunn, A., Bjerknes, C., and De Bodo, R. C. (1965). Effects of insulin on liver glycogen synthesis and breakdown in the dog. *American Journal of Physiology*, **208**, 307–316.
- Davidson, M. B., and Berliner, J. A. (1974). Effects of insulin in carbohydrate metabolism in rat liver slices: independence from glucagon. *American Journal of Physiology*, **227**, 79–87.
- Dershewitz, R., Vestal, B., Maclaren, N. K., and Cornblath, M. (1976). Transient hepatomegaly and hypoglycemia—a consequence of malicious insulin administration. *American Journal of Diseases of Children*, **130**, 998–999.
- Jefferson, L. S., Exton, J. H., Butcher, R. W., Sutherland, E. W., and Park, C. R. (1968). Role of adenosine 3'5' monophosphate in the effect of insulin and anti-insulin serum on liver metabolism. *Journal of Biological Chemistry*, **243**, 1031–1038.
- Madison, L. L. (1969). Role of insulin in the hepatic handling of glucose. *Archives of Internal Medicine*, **123**, 284–292.
- Mandell, F., and Berenberg, W. (1974). The Mauriac syndrome. *American Journal of Diseases of Children*, **127**, 900–902.
- Mortimore, G. E., King, E., Jr, Mondon, C. E., and Glimsman, W. H. (1967). Effects of insulin on net carbohydrate alterations in perfused rat liver. *American Journal of Physiology*, **212**, 179–183.
- Robison, G. A., Sutherland, E. W., and Butcher, E. (1971). *Cyclic AMP*, p. 130. Academic Press: New York.
- Rosenbloom, A. L., and Giordano, B. P. (1977). Chronic overtreatment with insulin in children and adolescents. *American Journal of Diseases of Children*, **131**, 881–885.
- Steele, R., Bishop, J. S., Dunn, A., Altszuler, N., Rathgeb, I., and De Bodo, R. C. (1965). Inhibition by insulin of hepatic glucose production in the normal dog. *American Journal of Physiology*, **208**, 301–306.

Correspondence to Professor Z. Laron, Institute of Paediatric and Adolescent Endocrinology, Beilinson Medical Centre, Petah Tikva, Israel.