Primary biliary cirrhosis after benoxaprofen

Benoxaprofen was withdrawn from use in 1982 because of reports of it causing fatal, cholestatic jaundice. We report three cases of primary biliary cirrhosis after benoxaprofen, an association not previously recognised.

Case reports

CASE 1

A 67 year old woman received benoxaprofen 600 mg/day for three months in 1981 for sciatica. A further course was given between April and June 1982, during which she developed a photosensitive rash and brittle nails. Shortly afterwards she was found to have raised serum alkaline phosphatase activity. From November 1982 she noticed increasing skin pigmentation, followed eight months later by jaundice and hepatomegaly. Follow up confirmed persistently abnormal liver function with a positive result on antimitochondrial antibody testing and liver histology compatible with primary biliary cirrhosis (table).

CASE 2

A 57 year old woman with rheumatoid arthritis received benoxaprofen 600 mg/day from December 1980 to June 1982, when she developed a generalised, pruritic rash that cleared when the drug was stopped, although pruritus persisted. In March 1983 she was admitted to hospital with deep jaundice, loss of weight and hepatosplenomegaly. The results of an antimitochondrial antibody test were positive; liver function deteriorated until her death 28 months after initial diagnosis.

CASE 3

A 62 year old woman with primary hyperparathyroidism was admitted to hospital in January 1983 with lethargy, nausea, and vomiting. She had received benoxaprofen 600 mg/day from April 1981 to March 1982, when she developed a pruritic rash; two months before this her liver function tests had yielded normal results. Follow up over 30 months confirmed persistently raised serum alkaline phosphatase activity despite normal concentrations of serum calcium and positive results on antimitochondrial antibody testing.

Comment

The cause of primary biliary cirrhosis remains unknown, but knowledge about the clinical course of the disease has changed in recent years with increasing awareness of a long presymptomatic phase. The factors leading to hepatic decompensation and presentation with symptoms are obscure, though several drugs, including arsenicals, chlorpromazine, methyltestosterone, and tolbutamide have been implicated.[1] Some reported cases had a history different from that of classic primary biliary cirrhosis, with a more rapid onset and complete or partial resolution after stopping the drug. Other patients, however, have developed progressive liver damage and portal hypertension.[1] In the early reports the antimitochondrial antibody test was not available, but more recently cases of primary biliary cirrhosis associated with drugs have been reported as positive for antimitochondrial antibody.[2,3] Our first two patients had classic primary biliary cirrhosis with the specific anti-M2 antimitochondrial antibody subtype present in serum. The third patient almost certainly had primary biliary cirrhosis despite the absence of histological confirmation.

Cholestatic jaundice is a well recognised complication of benoxaprofen treatment,[4] and, although the mechanism is unknown, it is probably related to high concentrations of benoxaprofen accumulating in elderly patients with impaired renal function. Renal function was normal in our patients, suggesting that a different mechanism may have been responsible for the development of primary biliary cirrhosis. Recently, drug metabolism has been shown to be abnormal in primary biliary cirrhosis, with 95% of patients exhibiting impaired sulphoxidation, and in the cases tested (1 and 2) this was clearly shown (table).[5] Impaired sulphoxidation may be a marker of more generalised abnormality of drug handling in primary biliary cirrhosis. This in turn may lead to decompensation and presentation of pre-existing disease in genetically susceptible people after exposure to a known cholestatic drug—for example, benoxaprofen.

We accept that our hypothesis on the mechanism of benoxaprofen induced primary biliary cirrhosis cannot be proved presently as no tests exist to confirm a causal relation. We think, however, that the occurrence of the three cases described is unlikely to represent a chance association and may provide an important clue to the pathogenesis of primary biliary cirrhosis.

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1 Zimmerman HJ. Liver injury induced by chemicals and drugs. In: Bockus HL, ed. *Gastroenterology*. III. Philadelphia: WB Saunders, 1976;229-341.
2 Prat JM, Pla RV, Mari ML. Cirrosis biliar primaria aparecida tras la ingesta prolonga de clorpromazina. *Rev Clin Esp* 1976;**142**:483-5.
3 Brown PJE, Lesna M, Hamlyn AN, Record CO. Primary biliary cirrhosis after long-term practolol administration. *Br Med J* 1978;i:1591.
4 Anonymous. Benoxaprofen [Editorial]. *Br Med J* 1982;**285**:459-60.
5 Olomu A, Clements D, Waring R, Elias E. Poor sulphoxidation in primary biliary cirrhosis. *Lancet* 1985;i:1504.

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Insulinoma producing progressive neurological deterioration over 30 years

Insulinomas classically present with recurrent neuropsychiatric episodes precipitated by fasting,[1] although the range of manifestations is wide.[2] We present a case in which progressive global neurological deterioration over 30 years was apparently due to an undiagnosed insulinoma.

Case report

A 48 year old woman was admitted in 1983 from a hostel for the mentally handicapped. She had been found unrousable in bed that morning and on examination she was deeply unconscious with brisk reflexes and extensor plantar responses. Blood glucose concentration was 1·0 mmol/l (18 mg/100 ml) and she rapidly regained consciousness after receiving an infusion of 50% glucose. On recovery she was found to be mute, withdrawn, and profoundly deaf, requiring considerable nursing care. She had a spastic gait but no evidence of peripheral neuropathy.

A full history was obtained from her father, who described her physical and intellectual development during childhood as normal: at 16 she could competently read and write and on leaving school she worked for a local pharmaceutical firm. Since then her intellect, personality, hearing, and speech had gradually deteriorated. On neurological assessment in 1973 she was found to be deaf, uncommunicative, and mentally retarded with mild right sided pyramidal signs; no diagnosis was established. In 1976 she could no longer be managed at home and entered the hostel. Thereafter she had increasingly frequent episodes of transient neurological disturbance: inappropriate affect, confusion, ataxia, dense right hemiparesis, opisthotonoid seizures, and unconsciousness were all noted at different times and attributed to a combination of transient ischaemic attacks, epilepsy, and anticonvulsant toxicity. These episodes tended to occur in the early morning and invariably resolved within a few hours. They were superimposed

Details of three female patients with primary biliary cirrhosis at presentation

Case No	Age	Latent period (months)	Aspartate transaminase in U/l (normal 5-45)	Alkaline phosphatase in U/l (normal 70-330)	Bilirubin in μmol/l (normal <22 μmol/l)	Antimitochondrial antibody	Ultrasound of biliary tree	Liver biopsy (Ludwig stage)	Sulphoxidation index[5]*
1	67	15	375	1876	70	1/1000	No obstruction	II	97·2
2	57	26	130	5375	175	1/300	No obstruction	II	124
3	62	22	50	693	15	1/320	No obstruction	—	—

*Sulphoxidation index[5]: <6=extensive metabolisers; 6-18=intermediate metabolisers; >18=poor metabolisers.
Conversion: SI to traditional units—Bilirubin: 1 μmol/l=0·05 mg/100 ml.

on a background of slowly progressive deterioration of mobility, personality, and intellect.

Neurological investigation included computed tomography, which showed cortical atrophy, and a non-specifically abnormal electroencephalograph, with much high voltage β activity. Random estimations of blood glucose concentrations were consistently normal except for one subnormal result in 1976 when it was thought that she had accidentally taken sulphonylurea tablets. Subsequent random blood glucose estimations were normal and this was not investigated further.

Inappropriate insulin secretion was confirmed by finding serum insulin concentrations of 9·3 and 10·2 mU/l during subsequent hypoglycaemic episodes.[3] Further episodes were effectively prevented by oral diazoxide. While undergoing investigation, however, she developed rapidly fatal septicaemia. At postmortem examination a well differentiated islet cell tumour, 15 mm in diameter, was found in the pancreas. Her brain was atrophic, and histological examination showed multiple focal infarcts of variable size in the cerebral and cerebellar hemispheres and basal ganglia, with relative sparing of the temporal lobes and hippocampus. In the cerebellum there was widespread loss of Purkinje cells.

Comment

An insidious and irreversible dementing process without acute episodes has been described with insulinoma but is rare; two major reviews of a total of 318 cases found evidence of irreversible neuropsychiatric deficit in only three cases.[2,4] The duration of symptoms before diagnosing insulinoma often exceeded 10 years,[1] and one well documented case presented with a history of over 25 years.[5] Such a delay in diagnosis is presumably more likely when the course is atypical or relatively benign.

We suggest that our patient's gradual global neurological deterioration since adolescence was the result of recurrent episodes of hypoglycaemia due to an insulinoma that had eluded diagnosis for over 30 years. This case illustrates the difficulty of detecting intermittent hypoglycaemia and the importance of excluding it with fasting blood samples in cases of progressive, unexplained neurological deficit.

1 Marks V, Samols E. Insulinoma: natural history and diagnosis. *Clinics in Gastroenterology* 1974;3:559-73.
2 Crain EL, Thorn GW. Functioning pancreatic islets cell adenomas. *Medicine (Baltimore)* 1949;28:427-47.
3 Turner RC, Heding LG. Plasma proinsulin, C-peptide and insulin in diagnostic suppression tests for insulinomas. *Diabetologia* 1977;13:571-7.
4 Service FJ, Dale AJD, Elveback LR, Jiang NS. Insulinoma: clinical and diagnostic features of sixty consecutive cases. *Mayo Clin Proc* 1976;51:417-29.
5 Nelson RL, Rizza RA, Service FJ. Documented hypoglycaemia for twenty-three years in a patient with insulinoma. *JAMA* 1978;240:1891.

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Predicting risk of diabetic ketoacidosis in patients using continuous subcutaneous insulin infusion

Several recent reports have discussed an increased incidence of diabetic ketoacidosis during continuous subcutaneous insulin infusion compared with conventional injection treatment.[1-3] The possibility that this increased incidence may be at least partly due to certain characteristics of the patients who use infusion treatment has not previously been explored.

Patients, methods, and results

During a feasibility study of the use of continuous subcutaneous insulin infusion in a diabetes clinic 11 patients were identified who had experienced episodes of diabetic ketoacidosis over a period of two years and six months while using the infusion treatment.[4] These patients were matched for age, sex, and duration of diabetes with 11 patients using continuous subcutaneous infusion who had not experienced ketoacidosis. All 22 patients had completed a series of newly designed psychological scales before starting the treatment. The psychometric development of these scales has been described elsewhere.[5] Ketoacidosis was defined as ketosis and hyperglycaemia with thirst, nausea, malaise and vomiting, and plasma bicarbonate concentration <15 mmol(mEq)/l.

The groups were compared for age at leaving full time education, daily insulin dosage and carbohydrate intake, duration of insulin use, initial and 12 monthly glycosylated haemoglobin concentrations and psychological measures. The psychological scales provided measures of perceived control of diabetes, which included five scales measuring internal versus external control and two scales measuring perceptions of medical factors affecting control. Scales measuring health beliefs specific to diabetes provided eight further variables. Independent group *t* tests were used for comparison between the two groups on all measures. The table shows the results.

Comparison of demographic, clinical, and psychological variables in patients who suffered episodes of ketoacidosis and those who did not. Values are means (SD)

	Developed ketoacidosis	Did not develop ketoacidosis	*t*	df	p
Demographic features					
Sex	7F:4M	7F:4M			
Age (years)	35·2 (13·8)	34·0 (13·1)	−0·21	20	NS
Age at leaving full time education	15·4 (1·3)	18·5 (3·6)	2·29	17	<0·05
Clinical and biochemical features					
Duration of diabetes (years)	13·9 (10·8)	14·2 (10·0)	0·06	20	NS
Daily insulin dosage (U/kg)	55·8 (21·5)	61·0 (19·7)	0·10	20	NS
Glycosylated haemoglobin (%):					
Initially	60·4 (9·2)	58·5 (12·2)	−0·39	20	NS
At 12 months	51·2 (6·9)	52·3 (7·8)	0·32	18	NS
Psychological features					
Perceived control scales*:					
Internality	23·9 (7·0)	25·1 (4·3)	0·47	17	NS
Personal control	22·8 (4·6)	27·7 (2·2)	2·98	16	<0·01
Foreseeability	17·9 (4·4)	24·2 (8·5)	1·92	17	0·071
Externality	12·1 (7·4)	10·2 (6·5)	−0·61	17	NS
Chance	12·7 (6·5)	11·1 (7·1)	−0·51	18	NS
Treatment	18·1 (4·0)	13·9 (4·5)	−2·09	17	0·052
Medical control	14·3 (6·3)	13·3 (7·4)	−0·30	17	NS
Health belief scales:					
Perceived severity†:					
Hypoglycaemia	3·4 (1·2)	4·4 (1·3)	1·88	20	0·075
Hyperglycaemic coma	5·4 (0·7)	5·5 (0·5)	0·71	20	NS
Perceived vulnerability†:					
Hypoglycaemia	5·0 (1·2)	4·4 (1·9)	−0·96	20	NS
Hyperglycaemic coma	4·2 (1·2)	2·9 (1·2)	−2·50	20	<0·05
Perceived severity of complications‡	20·7 (1·4)	21·1 (2·0)	0·49	20	NS
Perceived vulnerability to complications‡	15·0 (3·6)	15·4 (3·5)	0·24	20	NS
Perceived benefits of treatment§	26·1 (7·2)	28·8 (6·2)	0·95	20	NS
Perceived barriers to treatment§	16·5 (8·4)	12·0 (5·9)	−1·44	20	NS

*Scores ranged from 0 to 36: the higher the score the stronger the attribution towards the variable.
†Scores ranged from 1 to 6: the higher the score the greater the perceived severity or vulnerability.
‡Scores ranged from 4 to 24: the higher the score the greater the perceived severity or vulnerability.
§Scores ranged from 0 to 36: the higher the score the more benefits or barriers perceived.

Clinical and demographic measures did not differ between the groups, except for age at leaving full time education: patients who developed ketoacidosis had had significantly fewer years of full time education.

Psychological measures—Significant or nearly significant differences were obtained for three of the seven scales measuring perceived control—namely, personal control, foreseeability, and treatment. Compared with the patients who had not experienced episodes of ketoacidosis, those who had felt less personally in control of their diabetes, thought that outcomes were less foreseeable, and attributed more responsibility for diabetes management to the treatment. The health belief ratings indicated that patients who had had episodes of ketoacidosis tended to feel more vulnerable to problems related to their diabetes, differences between groups reaching significance for perceived vulnerability to hyperglycaemic coma. None of the differences in ratings of perceived severity of complications reached significance, although the patients who had had episodes of ketoacidosis tended to rate each problem as less severe.

Comment

The two groups of patients were distinguishable only by the psychological variables measured and age at leaving full time education, the patients who developed ketoacidosis having had fewer years of education. These patients seemed to be looking for a medical solution to their diabetes and considered that they personally had little control over the disease. Such patients may be less likely to detect metabolic problems and to initiate emergency action when necessary. Before using continuous infusion treatment the patients' who went on to develop ketoacidosis rated themselves as being more vulnerable to this complication, although prior experience of ketoacidosis was similar in both groups. These feelings of vulnerability might reflect their feelings of being less in control of their diabetes.

Over optimistic expectations of continuous subcutaneous infusion may have encouraged patients to assume that less personal responsibility for their diabetes would be required than with injection treatment. Ketoacidosis may, however, have arisen because of some characteristic of infusion treatment combined with the psychological characteristics identified here. Either way, this study indicates that patients' perceptions of their vulner-