Cholecystoparesis with Diabetic Autonomic Neuropathy


A 69-year-old male diabetic patient was hospitalized with pneumonia in February 1996. Abdominal ultrasonography performed as a routine examination on admission revealed marked dilatation of gallbladder with a fasting maximal size of 25.7 cm² compared with 8.8±2.9 cm² evaluated in 30 male healthy controls aged 67±8 years old. Four months after recovery from pneumonia, abnormal gallbladder dilatation remained unchanged (25.0 cm²), while dilatation had not been observed on an examination performed 6 years earlier (9.8 cm²). Because of accompanying neurological defects, we suppose that cholecystoparesis may be caused by progression of autonomic neuropathy in this patient with diabetes mellitus.

(Internal Medicine 36: 624-627, 1997)

Key words: diabetic neuropathy, cholecystomegaly, gallbladder, diabetes mellitus, autonomic nerve

Introduction

Patients with diabetes mellitus are thought to have a high risk of developing gallstones (1–3) because of the high incidence of obesity or the elevated saturation of the gallbladder bile with cholesterol (4). Furthermore, it is reported that the fasting gallbladder volume is increased and that postprandial emptying is inadequate in diabetic patients (5). This finding may be a key factor in the pathogenesis of gallbladder stones in patients with diabetes mellitus. Since the prevalence of diabetic autonomic neuropathy in patients with impaired gallbladder motility is significantly higher than that without neuropathy, most investigators agree the gallbladder dysfunction reflect diabetic autonomic neuropathy (6–11). This clinical entity has been called diabetic cholecystomegaly (5), diabetic neurogenic gallbladder (6, 7), and diabetic cholecystoparesis (12). Contrarily, it has been reported that gallbladder volume and contraction in diabetics are similar to those in normal subjects (13–16). Therefore, there are unresolved issues regarding diabetic gallbladder motility.

Here, we report a case of non-insulin-dependent diabetes mellitus (NIDDM) associated abnormal gallbladder dilatation which may be caused by autonomic neuropathy progressed during 6 years of observation.

Case Report

A 69-year-old Japanese male had been diagnosed as NIDDM in 1985. Family history included NIDDM in his daughter. He had received NPH insulin injection (20–34 units) from 1989, but glycated hemoglobin (HbA1c) levels had remained as high as 7.2–9.0% (normal range: 4.0–6.0). He developed numbness of the bilateral lower limbs in 1990. Because physical examinations revealed sensory disturbance including that of vibration sensation, diabetic peripheral polyneuropathy was diagnosed.

Here, we report a case of non-insulin-dependent diabetes mellitus (NIDDM) associated abnormal gallbladder dilatation which may be caused by autonomic neuropathy progressed during 6 years of observation.

From the Department of Internal Medicine, Shin-Koryo Hospital, Susaki, *the Second Department of Internal Medicine and **the Department of Radiology, Kochi Medical School, Kochi
Received for publication July 22, 1996; Accepted for publication May 15, 1997
Reprint requests should be addressed to Dr. Hiroyuki Itoh, the Second Department of Internal Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783
Diabetic Cholecystoparesis

palpable. The dorsal pedis arteries pulsed well on both sides. Neurological examinations revealed glove and stocking type disturbance of touch, pain and vibratory sensation in the peripheral extremities. Deep tendon reflexes were diminished. He showed preproliferative retinopathy on ophthalmological examinations.

Urinalysis revealed glucosuria and macroalbuminuria, 219 μg/min. The laboratory findings were as follows: erythrocyte sedimentation rate, 95 mm/h; red blood cell count, 399×10^4/μl; hemoglobin, 13.5 g/dl; white blood cell count, 4,700/μl with 65% neutrophils; platelet count, 30.7×10^4/μl; C-reactive protein, 5.9 mg/dl; serum level of total protein, 6.7 g/dl with 48% albumin and 23.2% γ-globulin; glutamic oxaloacetic transaminase, 31 IU/l; glutamic pyruvic transaminase, 13 IU/l; alkaline phosphatase, 187 IU/l (normal range: 72–265); γ-glutamyltranspeptidase, 40 IU/l (normal range <58); total bilirubin, 0.4 mg/dl; and amylase, 79 IU/l. Blood urea nitrogen level was 12 mg/dl, serum creatinine level, 0.7 mg/dl and creatinine clearance, 105 ml/min. The daily profile of blood glucose levels disclosed 147 mg/dl before breakfast, 228 mg/dl after breakfast, 131 mg/dl before lunch, 157 mg/dl after lunch, 94 mg/dl before dinner, 297 mg/dl after dinner, and 269 mg/dl before sleep. HbA1c value was 9.4%. Endogenous insulin secretion as urinary C-peptide immunoreactivity of 32.4 μg/24h was in the low normal range. Anti-glutamic acid decarboxylase antibody was negative. ECG revealed left ventricular hypertrophy. HRV on ECG recording was 3 beats/min at rest and 10 beats/min during deep breathing (normal range >10) (17, 18). QTc, QT time corrected for rate, was normal, 0.372 msec (19).

Abdominal ultrasonography showed abnormal gallbladder dilatation with a fasting maximal size of 25.7 cm² (long × short axis = 9.9×4.0 cm) on longitudinal scans of the right hypochondrium in the supine position (Fig. 1b), although it had been 9.8 cm² in August 1990 (Fig. 1a). After ingesting two egg yolks, the gallbladder contracted to 44% at 40 min (Figs. 2, 3), and the blood levels of cholecystokinin (CCK) were <7.5 pg/ml at the baseline, 9.5 pg/ml at 20 minutes, and 14.2 pg/ml at 60 minutes. Intramuscular injection of 0.3 μg/kg cerulein, which strongly affects gallbladder contraction similar to CCK, caused contraction to 51% at 20 minutes (Fig. 3). Blood levels of CCK were <7.5 pg/ml at the baseline, 23.8 pg/ml at 20 minutes, and 13.0 pg/ml at 60 minutes, respectively. There were no stones in the gallbladder or common bile duct (CBD) on abdominal ultrasonography and computed tomography. Dilatation of CBD or intrahepatic bile duct was not present. The urinary bladder showed residual urine over 100 ml and the prostatic gland showed a normal size by the measurement on ultrasonography.

According to these findings, NIDDM with cholecystoparesis and acute pneumonia was diagnosed. Intravenous administration of 2g cefotiam for 7 days and oral administration of 300 mg levofloxacin for 12 days improved pneumonia and the patient was discharged on March 3, 1996. After 1,600-kilocalorie daily diet therapy and subcutaneous NPH insulin injection of 20 units were initiated for NIDDM, the levels of blood glucose normalized to HbA1c of 7.1% in May and 7.1% in June 1996. Cholecystoparesis remained on follow-up abdominal ultrasonography with a fasting maximal size of 25.0 cm² (9.6×4.2 cm) in June.

Figure 1. Abdominal ultrasonography by longitudinal scan of the right hypochondrium in the supine position. (a) Maximal size of fasting gallbladder had been 9.8 cm² in August 1990. (b) It was increased to 25.7 cm² (9.9×4.0 cm) in February 1996.
Itoh et al

Figure 2. Changes in gallbladder size on real-time abdominal ultrasonography before and after ingesting two egg yolks. Gallbladder contracted to 44% at 40 minutes in comparison to the size before provocation.

Figure 3. Effect of egg yolk ingestion and intramuscular injection of cerulein on gallbladder size. Closed circles indicate percent gallbladder size after egg yolk ingestion. Open circles indicate percent gallbladder size after cerulein injection.

Discussion

Marumo et al (8) reported that fasting gallbladder dimensions were 11.3±6.8 cm² (mean±SD) in 56 Japanese diabetic patients and 9.1±2.2 cm² in 42 normal subjects. Our findings were 8.8±2.9 cm² in 30 normal male subjects (67±8 years). The fasting gallbladder size of the present patient was increased to 25.7 cm² in comparison with 9.8 cm² in 1990. Furthermore, gallbladder contraction after provocation with egg yolk revealed mild impairment (8). These results were not likely due to the organic diseases of the biliary tract, though we did not perform endoscopic retrograde cholangiopancreatography. Peripheral polyneuropathy in our patient was considered to be of diabetic origin since other diseases such as vitamin deficiency, alcoholism, amyloidosis, or uremia, could be ruled out. Therefore, we diagnosed this case as NIDDM with cholecystoparesis and peripheral neuropathy which had been persistent over the past 6 years, though we did not evaluate the autonomic nerve function in 1990.

Physiological gallbladder contraction and relaxation are regulated by both the endocrine and autonomic nervous system. Namely, CCK, which is one of gastrointestinal hormones, and the parasympathetic nerve evoke gallbladder emptying (20). Fasting gallbladder volume has been reported to be increased in diabetics with autonomic neuropathy in comparison to that in diabetic patients without autonomic neuropathy or in normal subjects because cholinergic action is diminished by disturbance of the celiac parasympathetic nerve (6-11). However, this theory remains controversial and has not been confirmed (13-16). Comparing with contradictory reports, patient ages in the former reports were higher than those in the latter reports, though most reports did not describe diabetes duration. Therefore, we consider that the varied prevalence of gallbladder dysfunction may depend on the differences in patient age or in the durations of diabetes mellitus. Furthermore, the previous reports were all cross-sectional studies and there were no longitudinal investigations for diabetic patients. The present case is the first to describe a NIDDM patient with cholecystoparesis under long-term follow-up. Therefore, we emphasize that this report is valuable to support the relationship between diabetic autonomic neuropathy and the presence of gallbladder dysfunction.

It has been confirmed that the parasympathetic nerve is involved in the early period and that the sympathetic nerve is...
disturbed in the later stage of diabetic autonomic neuropathy (21). Though the parasympathetic nerve was considered to be disturbed, the sympathetic nerve was intact in the present patient. Therefore, we suggest that the imbalance in sympathetic and parasympathetic regulation might exacerbate cholecystoparesis in our patient, but further prospective or retrospective investigations of this point are necessary.

The CCK response to egg yolk provocation is reported to be greater in diabetic patients with autonomic neuropathy than in normal subjects (11, 22). However, it is reported that hyperglycemia reduces CCK secretion (23). In the present patient, CCK secretion to egg yolk provocation was not enhanced, rather it was similar to that in normal subjects (11, 22). Furthermore, gallbladder motility in response to cerulein injection was intact in comparison to normal subjects in another report (24). Therefore, secretory defect of CCK or resistance to stimulation of CCK is not likely to be an important factor in gallbladder dysfunction in this case. Though we did not examine the responses of other gastrointestinal hormones on the provocation test, such as gastrin, secretin, motilin or pancreatic polypeptide, this would be necessary to evaluate the relationship between gallbladder dysfunction and the parasympathetic nerve.

Recently, it was reported that hyperglycemia directly causes gallbladder dysfunction (23, 25). Furthermore, improvement of gallbladder contraction within a month was reported following gallbladder dysfunction (23, 25). Furthermore, gallbladder motility in response to cerulein injection was intact in comparison to normal subjects in another report (24). Therefore, secretory defect of CCK or resistance to stimulation of CCK is not likely to be an important factor in gallbladder dysfunction in this case. Though we did not examine the responses of other gastrointestinal hormones on the provocation test, such as gastrin, secretin, motilin or pancreatic polypeptide, this would be necessary to evaluate the relationship between gallbladder dysfunction and the parasympathetic nerve.

References