Gall-bladder Dysfunction in Diabetes Mellitus

The Diabetic Neurogenic Gall Bladder

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Manifestations of autonomic neuropathy which occur in diabetes mellitus include nocturnal diarrhea or constipation with associated atony of the stomach and dysfunction of the small bowel, sphincter disturbances, atonic bladder, orthostatic hypotension, sudomotor and pilomotor disturbances, and impotence (see reviews by Joslin[1] and Rundles[2]).

Although only one of these disorders may be present, usually several occur together. Peripheral nerve involvement has also been present in the majority of the cases reported.

The diverse structures, functions, and locations of the organs affected suggest that the entire autonomic nervous system is vulnerable. It therefore seems possible that other, hitherto unrecognized, neurogenic syndromes may exist in diabetes. A deliberate search for such syndromes was undertaken and the findings concerning gall-bladder dysfunction in a group of unselected diabetic patients form the subject of this preliminary report.

MATERIALS AND METHODS

Cholecystography was performed in two groups of patients, using Telepaque or Biligrafin.

Group A consisted of thirty-five patients with diabetes mellitus of various degrees of severity.

Nine of these patients were males, thirty-six to seventy-four (mean sixty-three) years of age, and twenty-six were women, aged forty to seventy-two (mean fifty-nine) years. The insulin requirements of these patients varied between 0 and 72 units. Some were receiving tolbutamide treatment. None of the patients had ketosis or marked electrolyte disturbances during the period of examination.

Fourteen patients had symptoms and/or signs suggesting chronic cholecystitis or cholelithiasis, and two others had compensated liver cirrhosis of the Laennec type. In these sixteen patients abdominal discomfort, if present, was not severe.

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The remaining nineteen patients had no abdominal pains, and (with the exception of a nontender, palpable liver, in some cases) had no clinical or laboratory evidence of liver or biliary tract disease.

Ten patients, all with longstanding diabetes, had signs of peripheral neuropathy and proliferative retinopathy. Two of these patients suffered from intermittent diarrhea of nocturnal type, with anal sphincter disturbances. There was no obvious cause for the diarrhea, but since they also had other signs of autonomic nervous system involvement, such as sweating disturbances, orthostatic hypotension, or bladder troubles, the diagnosis of "diabetic diarrhea" was made. Nine of these patients had no symptoms of gall-bladder disease.

Group B consisted of forty-five nondiabetic patients whose age and sex were comparable with those of the diabetic group. Most of these patients came for investigation of disorders not related to the biliary system and had no signs or symptoms of disease of this system. In all of them the gall bladder was well visualized and no stones were discernible.

The degree of visualization of the gall bladder, its size and contraction after a standard fatty meal in the diabetic group, were compared with those in the nondiabetic individuals. For comparison of the gall-bladder size, the surface of the X-ray shadow of the viscus was calculated arbitrarily as half of the product of its largest transverse diameter by its length (surface of two triangles with a common base).

The measurements of the gall-bladder shadow were made "blind," i.e., made without knowing the diagnosis of the patients.

RESULTS

These are illustrated by tables 1 and 2.

1. *Nondiabetic individuals (Group B)*

(a) The mean surface of the gall-bladder shadow was 16.6 sq. cm. (table 1). Gall bladders with an equal or smaller surface were considered of "average" size, and larger—as "large." (b) There was no apparent correlation between the size of the gall bladder and sex or age of the patients. Almost half of these patients had large gall bladders (table 2). (c) The mean surface

TABLE 1

The size of the gall-bladder shadow in diabetic and nondiabetic patients, before and after a standard fatty meal

Patients	Number of cases	Gall-bladder surface *before* meal (sq. cm.) mean ± S.E.	Gall-bladder surface *after* meal (per cent of initial surface) mean ± S.E.
Nondiabetic individuals with no sign of gall-bladder disease	45	16.6±0.8	56.9±2.8
Diabetic patients with visualized gall bladder and no evidence of gall stones	25	23.3±1.6 S: $p<0.01$*	61.8±1.8 NS: $p>0.05$†
Diabetes with neuropathy, retinopathy, visible gall bladder and no evidence of gall stones	7	29.2±2.8 S: $p<0.01$*	71.1±5.0* S: $p<0.05$

*S = Significant difference in relation to nondiabetic individuals

†NS = No significant difference.

TABLE 2

The X-ray appearance of the gall bladder in thirty-five diabetic patients and in forty-five nondiabetic subjects

X-ray findings	Diabetics, the whole group	Diabetics with neuropathy and retinopathy	Nondiabetics with no signs of gall-bladder disease
All cases	35	10	45
Gall stones visible	5	2	0
Gall stones not visible	30	8	45
Visualization of gall bladder			
Good	21	3	45
Poor or not visible	9	5	0
Size of gall bladder			
Average	4	0	24
Large	21	7	21
Contraction after fatty meal			
Average	8*	2	22
Less than average	14	5	23

*Only twenty-two cases are listed as in three cases the gall-bladder shadow could not be identified after fatty meal.

of the gall-bladder shadow after the fatty meal was 56.9 per cent of its original surface (table 1). Half of the patients had a smaller contraction (table 2).

2. *Diabetic patients (Group A)*

(a) Gall stones were detected in five patients (table 2). (b) Of the remaining thirty patients, the gall bladder was visualized in twenty-five, in twenty-one of them well or fairly well (tables 1 and 2). (c) Most of the diabetics had a "large" gall bladder, and the proportion of cases with poor contraction after a fatty meal was significantly greater than in the control individuals (tables 1 and 2). Poor contraction was often associated with large size of the gall bladder. (d) The proportion of patients with poorly visualized, large and poorly contracting gall bladders was greater in the ten diabetic patients with neuropathy and retinopathy than in the whole diabetic and the nondiabetic groups (tables 1 and 2). Each of these ten patients had two or more of the four signs in consideration: stones, large, poorly contracting or poorly filling gall bladder. (e) Poor contraction, poor visualization and large size of the gall bladder were as frequent among patients with symptoms and signs of gall-bladder disease as among those without them.

DISCUSSION

Due to the small number of patients in this study, no attempt was made to determine statistical validity as to the frequency and type of gall-bladder disease in diabetics when compared to nondiabetic individuals. However, some of the findings seem unlikely to be fortuitous, and they warrant further study.

The frequent occurrence in the diabetic group of large, poorly contracting and poorly filling gall bladders is remarkable. This is especially so as there were no signs of gall stones or of inflammatory disease of the biliary tract in half of these patients.

There is much to suggest that such signs may develop on a purely neurogenic basis and that, at least in some of the patients, they resulted from diabetic neuropathy.

1. *Poor contraction of the large, well visualized gall bladder*

It is well established that biliary stasis, with distension of the gall bladder and bile ducts and associated with pains and other signs of gall-bladder dysfunction, may occur in the absence of organic disease of the biliary tract or of adjacent structures.[3-7]

This type of disorder has been termed "biliary dyskinesia,"[3] "biliary dyssynergia"[4] and "biliary vesicular stasis."[5] In some cases "autonomic imbalance" has been incriminated as the cause.[6] This view is supported by experiments which have shown that nervous stimulation or denervation of the gall bladder and of the sphincter of Oddi, or the administration of sympathico- and parasympathicomimetic drugs, affect the shape and the contraction of the gall bladder.[3,7-9]

Biliary dyskinesia is of two types: (a) hypertonic, caused by hypertony of the sphincter of Oddi, and (b) hypotonic, resulting from atony of the gall bladder itself ("the lazy gall bladder"). In both types an en-

larged, well visualized but poorly contracting gall bladder is a common finding.[5,6]

We have been able to follow the gall-bladder changes over a period of seven years in a sixty-six-year-old female diabetic patient with longstanding diabetes and neuropathy and retinopathy. The patient had pains in the right upper quadrant of the abdomen and a palpable and tender liver. From the beginning the gall bladder was large and well visualized and its size progressively increased. Its surface before and after fatty meal was, respectively, as follows: 1954—43.7 sq. cm., 42 per cent; 1956—49.0 sq. cm., 51 per cent; 1960—52.5 sq. cm., 23 per cent; 1961—79.8 sq. cm., 72 per cent.

A similar increase in size of the well visualized gall bladder, with intermittent loss of contraction power in the latter stage, was also noted in another woman. This forty-five-year-old patient suffered for many years from abdominal pains suggesting gall-bladder disease. However, no organic disease of the viscus or of adjacent structures has been found on exploration. The patient later developed mild diabetes.

Both patients probably suffered from "biliary dyskinesia." They resemble the case recently reported by Rose[5] as a typical case of "biliary vesicular stasis" of the hypotonic type. During surgical exploration of these types of cases, Rose frequently found a distended, elongated gall bladder which evacuated freely into the duodenum through a widely open sphincter of Oddi:

Additional support for theory that autonomic neuropathy may lead to dysfunction in an otherwise normal gall bladder is provided in our own experiments in which hexamethonium in large doses was given to a 22-kg. dog. The aim was to simulate autonomic neuropathy, for this drug, given in sufficiently high doses, causes orthostatic hypotension, inhibition of the intestinal motor activity, urinary retention and impotence. Such a picture resembles that seen in patients with diabetic autonomic neuropathy, and also after sympathectomy. Hexamethonium thus induces a kind of "medical neuropathy" resembling true autonomic neuropathy.

When the dog was injected with 50 mg. hexamethonium iodide there was no contraction of the well visualized gall bladder (20 cc. of 50 per cent Biligrafin, intravenous) one hour after a fatty meal. Good contraction was noted twelve hours later. In a control experiment without hexamethonium, good gall-bladder contraction was found one hour after a similar meal. Daily peroral administration of 1.2 to 2.4 gm. hexamethonium bitartrate over a two-week period resulted in both poor contraction and poor visualization of the gall bladder. This was seen in repeated experiments. In one of these, 0.25 mg. carbaminoylcholine was injected intramuscularly after the gall bladder had failed to contract following the meal. This resulted in normal contraction of the viscus.

The clinical findings in biliary dyskinesia, the experimental data reported in the literature, and our observations suggest that poor contraction of a well visualized gall bladder and its large size could be characteristic signs of the "neurogenic gall bladder."

2. *Poor visualization of the gall bladder*

Poor visualization of the unobstructed gall bladder occurs when the viscus is inflamed. Logically, it should also occur with the atonic neurogenic gall bladder, even if the mucosa is intact, for the resultant stagnation of bile will impair or prevent the inflow of fresh liver-bile containing the contrast medium. Similarly, if the sphincter of Oddi is atonic, the dye will flow freely into the duodenum and bypass the gall bladder. In both cases the gall bladder will not be well visualized with X rays.

Whether or not autonomic neuropathy may also impair visualization of the gall bladder by affecting the ability of its mucosa to concentrate bile and contrast dye, has yet to be determined.

It may also be inferred from the above that poor visualization may also be a sign of autonomic neuropathy of the gall bladder.

3. *The symptomless pathological gall bladder*

Biliary pains and other symptoms are caused by inflammation, or by excessive contraction of the biliary tree and of the gall bladder.[9] It may be argued that atony of an otherwise normal gall bladder and of the sphincter of Oddi will not induce pain, unless infection and inflammation supervene. Thus, such a gall bladder will appear pathological on X-ray examination, but will remain "silent" clinically. This is known to be the case with the neurogenic urinary bladder.

Theoretically, neuropathy may also involve sensory elements supplying the biliary tract. This would modify or abolish pains associated with disease of this system. Paravertebral block, splanchnicectomy or celiac ganglionectomy are capable of relieving biliary pain.[9]

One may therefore infer that absence of symptoms of gall-bladder disease may also be a feature of the diabetic neurogenic gall bladder. This may perhaps explain the occurrence of "silent" empyemas and perforations of the gall bladder in diabetics.

4. *The diabetic neurogenic gall bladder*

In the light of the above-mentioned considerations, the existence of the neurogenic gall bladder seems to be very probable. Its signs would be a large, poorly contracting and/or poorly visualized and often symptomless gall bladder.

Many of our diabetic patients had several of these signs but to prove that they were caused by autonomic neuropathy is difficult. The evidence in the literature for the neurogenic etiology of other disorders (e.g., diabetic diarrhea or constipation) is often purely cir-

cumstantial.[10] The diagnoses were based mainly on the absence of specific causes, and on the presence of such concomitant, obvious signs of involvement of the nervous system as peripheral neuropathy, orthostatic hypotension, sweating disturbances, and impotence.

On applying similar criteria to our diabetic patients, it might be assumed that the ten who had obvious signs of nervous system involvement and retinopathy would be the most likely to develop the neurogenic gall bladder. In fact, cholecystography disclosed changes compatible with this diagnosis in at least seven of these patients, none of whom had signs or symptoms of inflammatory disease of the biliary tract. In only one of the ten patients had cholecystography been thought necessary prior to the present study.

Kozoll[11] suggested that cholecystography should be routinely performed in diabetic patients. He also considered that cholecystectomy should be undertaken when evidence of nonfunctioning gall bladder is demonstrated. However, caution seems necessary before advising surgery in these cases, for it is considered contraindicated in biliary dyskinesia.[6] Choline derivatives might perhaps be worth a trial in view of the results obtained in the above-mentioned dog experiments. It may be mentioned that Urecholine has been used in the treatment of neurogenic urinary bladder.

The frequently observed coincidence of gall-bladder dysfunction and neuropathy with diabetic retinopathy raises the question whether microaneurysms and venous dilatations in the retina[1,12] as well as in conjunctiva and nail beds[13] could result from patchy denervation due to autonomic neuropathy. The finding by Wolter of pathological nerve fibers around microaneurysms and venules[14] may perhaps have a bearing on such a hypothesis.

The results of this search for the diabetic neurogenic gall bladder seem to warrant further study of this disorder, and of manifestations of autonomic neuropathy in other contractile organs and secretory glands in a large series of patients.

SUMMARY

1. The size of the gall-bladder X-ray shadow and degree of its visualization and contraction after a standard fatty meal were determined in two groups of patients: in thirty-five unselected diabetics, sixteen of whom had symptoms suggestive of gall-bladder disease, and ten of whom had neuropathy and retinopathy; and in forty-five nondiabetics without symptoms or signs of gall-bladder disease.

2. Large, poorly contracting and often poorly filling gall bladders were frequent among the diabetics, regardless of the presence or absence of symptoms of gall-bladder disease. These signs were especially frequent in patients with diabetic neuropathy and retinopathy and less frequent in the nondiabetics.

3. The occurrence of a "diabetic neurogenic gall-bladder" syndrome has been postulated. The signs of this syndrome are considered to be: large size, poor contraction and/or poor visualization of the gall bladder, and lack of symptoms of gall-bladder disease.

4. The pathogenesis of this disorder and its relation to other known and unknown neuropathies in diabetes are discussed.

SUMMARIO IN INTERLINGUA

Dysfunction del Vesica Biliari in Diabete Mellite: Le Vesica Biliari Diabetico-Neurogene

1. Esseva determinate le magnitude del umbra radiographic del vesica biliari e le grado de su visualisation e contraction post un repasto standard a grassia in duo gruppos de patientes: In trenta-cinque non-seligite diabeticos (incluse dece-sex con symptomas suggestive de morbo del vesica biliari e dece con neuropathia e retinopathia) e in quaranta-cinque non-diabeticos sin symptomas o signos de morbo del vesica biliari.

2. Grande vesicas biliari, con imperfecte contraction e frequentemente imperfecte replenation, esseva commun inter le diabeticos, sin reguardo al presentia o absentia de symptomas de morbo del vesica biliari. Iste signos esseva particularmente frequente in patientes con neuropathia e retinopathia diabetic e minus frequente in le nondiabeticos.

3. Es postulate le occurrentia de un syndrome de "vesica biliari diabetico-neurogene. Es opinate que le signos de iste syndrome es: grande dimensiones, imperfecte contraction e/o imperfecte visualisation del vesica biliari, e absentia de symptomas de morbo del vesica biliari.

4. Le pathogenese de iste disordine e su relation con altere cognoscite e non-cognsocite neuropathias in diabete es discutite.

REFERENCES

[1]Joslin, E. P., Root, H. F., White, P., and Marble, A.: The Treatment of Diabetes Mellitus. Philadelphia, 10th Edition, Lea & Febiger, 1959, pp. 483-503, 547, 550.

[2]Rundles, R. W.: Diabetic neuropathy. Bull. N.Y. Acad. Med. 26:598, 1950.

[3]Ivy, A. C. and Sandblom, P.: Biliary dyskinesia. Ann. Intern. Med. 8:15, 1934.

[4]Best, R. R. and Hicken, N. F.: Biliary dyssynergia: physiological obstruction of the common bile duct. Surg. Gynec. Obstet. 61:721, 1935.

[5]Rose, J. D.: Biliary vesicular stasis. Lancet 1:1356, 1958.

[6]Twiss, J. R. and Oppenheim, E.: Practical Management of

Disorders of the Liver, Pancreas and Biliary Tract. Philadelphia, Lea & Febiger, 1955, pp. 81-93.

[7]Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts. Philadelphia, 2nd Edition, Lea & Febiger, 1949, pp. 991, 1032-35, 1000.

[8]Popper, H. and Schaffer, F.: Liver: Structure and Function. New York, Blakiston Division, McGraw-Hill Book Co., 1957, pp. 17, 118.

[9]Sterling, J. A.: The Biliary Tract. Baltimore, Williams & Wilkins, 1955, pp. 59, 60, 362.

[10]Berge, K. G., Sprague, R. G., and Bennett, W. A.: The intestinal tract in diabetic diarrhea. Diabetes 5:289, 1956.

[11]Kozoll, D. D., Dwyer, G., and Meyer, K. A.: Pathologic correlation of gall stones. Arch. Surg. 79:514, 1959.

[12]Ashton, N.: Diabetic retinopathy. Lancet 2:625, 1958.

[13]Landau, J. and Davis, E.: The small blood vessels of the conjunctiva and nail bed in diabetes mellitus. Lancet 2:731, 1960.

[14]Wolter, J. R.: Diabetic capillary microaneurysms of the retina. Arch. Ophthal. 65:847, 1961.

Detection of Galactosemia

Galactosemia is a genetic disease in man in which galactose from any source in the diet cannot be metabolized and hence accumulates in the blood. The metabolic block has been identified as the absence of galactose-1-phosphate uridyltransferase activity (*Nutrition Reviews* 17:115, 1959).

The primary problem is early detection of the disease. If milk is removed from the diet within a few days of birth, the symptoms of galactosemia can be prevented. These include jaundice, enlarged liver, and eventually cataracts and mental deficiency. Most laboratory tests for this disease are too complicated and expensive to be used routinely. The availability of rapid, simple detection methods would aid in routine testing for this uncommon condition.

A commonly used diagnostic procedure for galactosemia is the galactose tolerance test. This is not specific, however, and may be harmful to the patient. Other methods measure the galactose-1-phosphate uridyltransferase activity of erythrocytes, either by measuring oxygen uptake manometrically (V. Schwarz, A. R. Wells, A. Holzel, and G. M. Komrower, *Ann. Human Genetics* 25:179, 1961) or by measuring the production of carbon dioxide from galactose-1-C^{14} via the hexose monophosphate pathway (A. M. Weinberg, *Metabolism* 10:728, 1961). These methods distinguish the galactosemic patient from the heterozygous carrier as well as from the normal individual but require equipment which may not be available in a clinical laboratory.

More recently a test paper specific for the detection of very small amounts of galactose and galactose-containing sugars has been reported (E. S. Rorem and J. C. Lewis, *Anal. Biochem.* 3:230, 1962). Although this test was developed to determine the galactose content of plant and other food material, it may be possible to adapt the test paper to determine galactose levels in blood or urine.

The procedure described by Rorem and Lewis uses galactose oxidase grown from cultures of the fungus *Polyporus circinatus* Fr. The crude enzyme is prepared by freeze-drying of the previously filtered and dialyzed culture medium. The enzyme, in the presence of oxygen, catalyzes the oxidation at carbon six of galactose from an alcohol to an aldehyde with the formation of hydrogen peroxide. The test papers are prepared from filter paper treated with o-tolidine. One end of the paper is dipped into a solution of the galactose oxidase enzyme, horse-radish peroxidase, and Carbowax 6000 in phthalate buffer. After drying in the dark, the papers are ready for use. The finished paper has a light tan color which turns deep blue-green when dipped into a solution containing galactose. As little as 0.01 per cent α-D-galactose gives a positive response in ten minutes at 25° C. Raffinose is detected in ten minutes in solutions containing 0.04 per cent raffinose pentahydrate; shorter times are required for higher concentrations. Lactose is also detected, but only at higher concentrations. With lactose, the first traces of color appear in seven minutes with a 1 per cent solution and at thirteen minutes with a 0.5 per cent solution. The authors suggest that the test can be made semiquantitative by comparison with known sugar solutions.

Fluoride and chloride ions, as well as ascorbic acid, interfere in color reactions of this type. These substances can be removed from unknown solutions by de-ionizing with Amberlite ion-exchange resins. The column effluent may contain hydrogen peroxide which can be eliminated by adding the enzyme catalase to the effluent, and then inactivating the catalase by heating on a steam bath.

Rorem and Lewis have demonstrated that this simple and sensitive test can be used to detect galactose in food materials, whether free or in combined form. It would be of interest to determine whether this test paper could be used in detecting the galactosemia of infancy.

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