A Clinical Algorithm to Determine the Etiology of Brittle Diabetes

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Brittle diabetes is a subset of insulin-dependent diabetes mellitus for which multiple causes have been suggested. In its most severe form, brittle diabetes is incapacitating, preventing gainful employment and a normal lifestyle. Although some brittle diabetic individuals will significantly improve by intensive insulin therapy and education, many others remain unable to function normally because of recurrent episodes of hyperglycemia and hypoglycemia. We studied 30 incapacitated brittle diabetic subjects and developed an efficient algorithmic approach to determine the etiology of brittleness. Central to our diagnostic algorithm was the glucose response to 0.1 U/kg insulin administered subcutaneously and intravenously. If this response was normal, then psychosocial evaluations were completed, including psycholinguistic and health psychological testing. Other parameters affecting blood glucose concentration were also assessed, such as gastric motility, counterregulatory hormones, and, most important, patient compliance with prescribed regimens. However, if an "abnormal" glucose response to the insulin challenge tests was observed, the location of the insulin resistance was identified as being subcutaneous, intravascular, or at the peripheral tissue. Using our diagnostic algorithm, the identification of the etiology of brittleness in 29 of the 30 referred patients was possible. Thus, the purpose of an algorithmic approach to diagnosis is not only to avoid unnecessary testing, but also to determine the correct etiology of the brittle diabetes to determine appropriate therapy. DIABETES CARE 1985; 8:5–11.

The term "brittle diabetes" was coined by Woodyatt in 1934 to describe diabetic individuals whose blood glucose concentration fluctuated widely despite appropriate medical management.[1] Subsequently, Colwell,[2] Molnar,[3,4] and Service[5] described other subjects with brittle diabetes and provided a list of potential causes of wide swings in blood glucose concentration in insulin-dependent diabetes. These causes were re-emphasized in a comprehensive review by Tattersall in 1977.[6] In his review, Tattersall redefined brittle diabetic individuals as those "whose life is constantly being disrupted by episodes of hypo- or hyperglycemia, whatever their cause." We concur with the latter definition, since it is the incapacitated diabetic individual with a disrupted lifestyle who not only seeks, but urgently requires, medical diagnosis and treatment.

Since the identification of the subset of "brittle" diabetic individuals in 1934, much has been learned about the regulation of blood glucose concentration. Although not completely understood, many diverse factors are known to contribute, ranging from the rate of intestinal absorption of foodstuffs[7] to the presence of anti-insulin-receptor antibodies.[8] Much of the knowledge concerning the determinants of blood glucose concentration has only recently become available, following the development of sophisticated isotopic radiologic techniques and the refinement of hormonal assay methodologies for C-peptide, free insulin, and cellular insulin receptors. Faced with an almost unlimited number of diagnostic measurements and procedures to investigate the determinants of blood glucose concentration in individual brittle diabetic individuals, it has become necessary for the physician to use an efficient method of exclusion to arrive at an appropriate etiologic diagnosis of brittle diabetes. This algorithmic (or stepwise) approach is currently being used to establish other diagnoses,[9] but has not yet been applied to the assessment of the brittle diabetic individual. From our experience with 30 type I diabetic subjects referred for incapacitating brittle diabetes, an efficient algorithmic approach has been developed.

It must be emphasized that the diabetic individuals whom we recommend be entered into the diagnostic algorithm are

those who have not responded to intensive insulin management programs.[10] Intensive insulin therapy (including diet and exercise instruction), which is now widely used throughout the United States and Europe, will improve insulin control in the majority of insulin-dependent diabetic individuals.[11] In fact, it is unlikely that one or two injections of only intermediate- or long-acting insulin per day will maintain acceptable glucose control in any C-peptide–negative diabetic individual. The advantage of intensive insulin therapy regimens as the initial approach to brittle diabetes is that hospitalization is not required and that some individuals will no longer be "brittle." However, for the remainder of the individuals who continue to be incapacitated by recurrent hyper- or hypoglycemia, despite the best attempts of the physician and health care team,[12] a systematic, efficient approach aimed at identifying the etiology of the brittleness must be used. The 30 patients from which the following algorithm was derived had all been on intensive insulin therapy regimens for at least 1 yr without success, as defined by the inability of these patients to remain out of the hospital long enough to carry on a normal lifestyle, be it attending school, working, or raising a family.

DIAGNOSTIC APPROACH

(1) The subjects were admitted to the hospital for testing and placed under close observation (Figure 1). Routine studies were performed to exclude acute or chronic disease that may alter glucose metabolism. The history and physical examination may provide important clues as to chronic diseases affecting intermediary metabolism, such as hypoadrenalism, Cushing's disease, or pheochromocytoma. Frequently overlooked in the initial exam is the urinary drug screen, particularly for narcotics and barbituates; withdrawal symptoms can precipitate diabetic ketoacidosis. Two of our subjects were addicted to narcotics and exhibited withdrawal symptoms during hospitalization. A C-peptide–stimulation test should also be performed to assess endogenous insulin secretion.[13] If endogenous insulin secretion is present, factitious (self-induced) disease should be suspected since in one series, all ketoacidosis-prone diabetic patients were C-peptide negative.[14]

(2) Direct insulin challenge testing is the crux of the evaluation of the brittle diabetic subject, and its results determine the subsequent series of diagnostic tests. The reason for using a direct (prospective) insulin challenge rather than a retrospective review of the subjects' glucose records is that a comparison can be made with the glucose response to the same dose of insulin given to nonbrittle C-peptide–negative diabetic subjects. Figure 2 demonstrates the nonbrittle diabetic subjects' mean plasma glucose response to an insulin challenge test of 0.1 U/kg short-acting insulin given both subcutaneously and intravenously. In the diabetic individual, the maximal decline in blood glucose concentration should exceed 95 mg/dl by the subcutaneous route and 62 mg/dl by the intravenous route (mean response minus 2 SD). In the 10 stable type I diabetic subjects' data, shown in Figure 2, the range of decline of glucose responses for the subcutaneous route was 124–227 mg/dl (mean ± SD = 171 ± 38) and for the intravenous bolus insulin dose, 91–215 mg/dl (mean ± SD = 140 ± 39). Before giving the challenge dose of insulin in the morning, the overnight maintenance dose of continuous intravenous insulin infusion was discontinued for approximately 2 h until the blood glucose concentration exceeded 250 mg/dl.[15] All insulin was injected from a new bottle by a physician. No food was permitted 12 h before or during the study. Of the 30 patients studied, the majority (90%) demonstrated a normal response to both subcutaneous and intravenous challenge tests of insulin and were evaluated according to the left side of Figure 1. The remaining patients (10%) demonstrated a blunted insulin response to either (or both) the subcutaneous or intravenous insulin challenge testing and were evaluated according to the right side of Figure 1. Obesity per se is usually associated with systemic insulin resistance, and seven of the 30 subjects referred to us were >20% above ideal body weight. Six of these patients exhibited normal declines in blood glucose concentration during insulin challenge tests of 0.1 U/kg. The seventh patient had a blunted response and was subsequently diagnosed as having a cellular insulin postreceptor defect. However, since our experience with obese brittle diabetic individuals is limited, caution was exercised in interpreting an abnormal response as systemic resistance sufficient to cause brittle diabetes.

(3) If glucose responsiveness to insulin challenge testing was normal, we next assessed the language/learning (communication) abilities of the diabetic patient, not only to establish that the patient understands and can follow the directions of the health care team, but also to exclude as far as possible intentional noncompliance. Psycholinguistic and psychoeducational batteries delineate areas of deficit in the patient's knowledge and use of concepts. Psycholinguistics has been defined as "the underlying knowledge and abilities which people must have in order to use language."[16] The psycholinguistic evaluation involves a series of tests performed by a qualified speech-language pathologist or psychologist.[17,18]

(4) If deficits are identified during psycholinguistic evaluation, a program for remediation or compensation for these deficits must be established. For example, if the patient has a deficit in auditory processing (such as being able to hear the instructions but unable to comprehend them), but has normal visual processing ability, recommendations are made for instructions relating to the subject's diabetes care to be presented in writing in addition to the verbal communication. Different anatomic areas of the human brain are involved in processing information, and specific deficits are not uncommon. Much effort has been devoted to identifying these specific areas and treatment of deficits is aimed at enhancing specific processing skills.[19] Twenty-three percent of the brittle diabetic subjects we studied had significant communication deficits.

(5) The health psychological evaluation assesses the health locus of control, intensity of depression, and attitudes toward diabetes and health care providers.[20,21] The term "health

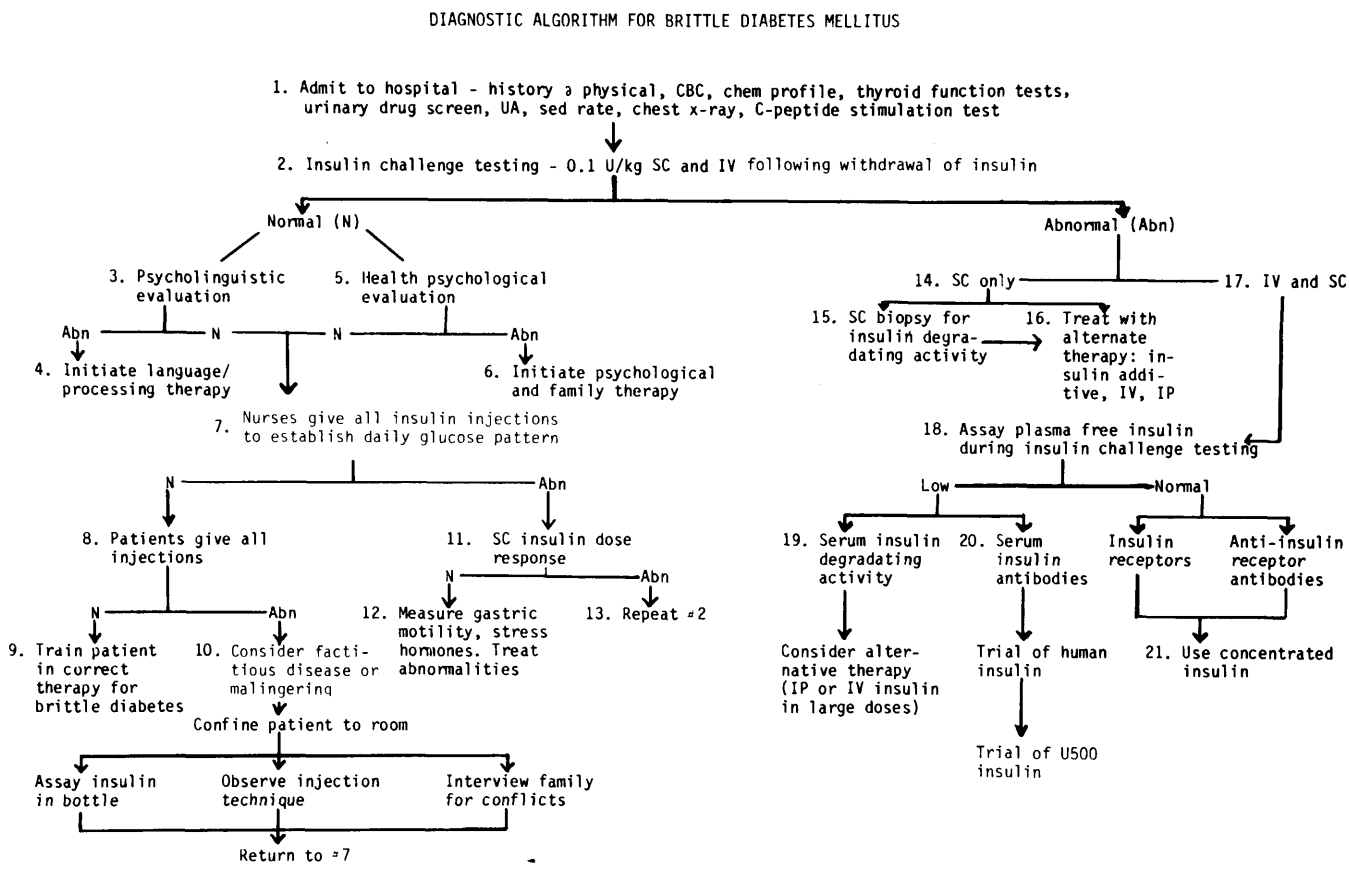

FIG. 1. A diagnostic algorithm to determine the etiology of brittle diabetes mellitus. The numbers refer to the correspondingly numbered sections in the text. The normal (i.e., nonbrittle type I diabetic volunteers) response to 0.1 U/kg insulin described in step 2 is shown in Figure 2.

locus of control" indicates the patient's assessment of who or what controls his diabetes. Thus, an "internal" health locus of control indicates that the patient believes his own actions (e.g., taking insulin, eating, or exercising) are responsible for the changes in his blood glucose concentration, whereas an "external" health locus of control indicates that he believes that other persons (such as physicians, nurses, parents, spouses) control his diabetes. A "chance" health locus of control indicates that the patient believes his diabetes is regulated by forces beyond his control (for example, luck, fate, and chance). Testing of the health locus of control has been standardized and is an important aspect of the evaluation to establish whether the patient believes that his actions have an influence on the control of his diabetes.[22] Without an appropriate health locus of control, the patient may not take appropriate action when his glucose is elevated. The field of behavioral medicine has greatly expanded during the last decade, and many formal testing procedures are available to identify behavior that may adversely affect diabetes. Testing should be done by a qualified individual to ensure reliable results from which specific treatment recommendations can be made. (The reader is referred to several recent texts for a more detailed discussion of this topic and a representative list of testing procedures and their interpretation.[23–25])

(6) If significant pathology is revealed during the health psychological evaluation, initiation of psychotherapy, which may involve both the family members and medical team, is recommended.[26] We strongly recommend involvement of psychologists experienced in behavioral modification, since in one large review, the best success in improving compliance was achieved by combining both an educational and a behavioral modification approach.[27] Of the subjects referred to us for evaluation, 53% had behavioral abnormalities sufficiently severe to adversely affect diabetes management.

(7) If the psycholinguistic and health psychological evaluations are within normal limits (or there are doubts that the abnormalities identified are the etiology of the brittle diabetes), then the daily pattern of glucose response to injected insulin is next established. To be sure that this is done correctly, all insulin must be injected by an experienced nurse, preferably in the subcutaneous tissue of the abdomen, where absorption is most reproducible. Only short-acting insulin is used, mild exercise (walking) is encouraged, and meals are provided on a 4–6-h schedule. To match the rise in plasma free insulin to the absorption of foodstuffs from

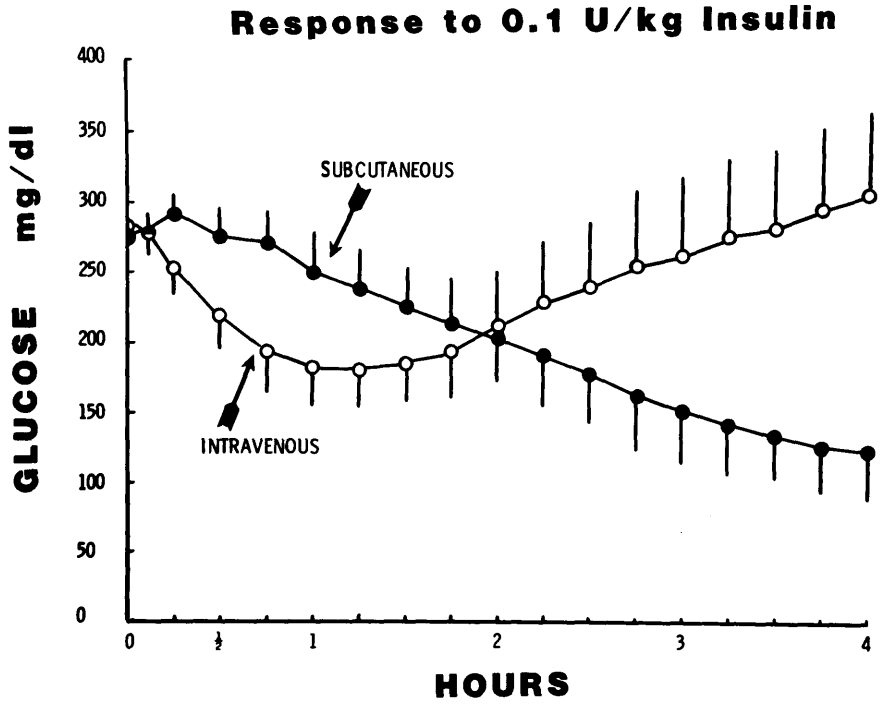

FIG. 2. The mean decline in blood glucose to a challenge dose of insulin (0.1 U/kg) administered subcutaneously or intravenously in 10 stable type I diabetic subjects. Although the decline in blood glucose is more rapid when the insulin is given intravenously compared with subcutaneously, the magnitude (from zenith to nadir) of the change should be at least 62 mg/dl by the intravenous route and 95 mg/dl by the subcutaneous route (mean response minus 2 SD). The range of responses in the 10 stable diabetic subjects was 91–215 mg/dl by the intravenous route and 124–227 mg/dl by the subcutaneous route.

the gut, the insulin is injected 15 min to a half-hour before meals on a 4–6-h schedule. In our experience, the biologic activity of short-acting insulin is not sufficient to suppress plasma glucose concentration for more than 5 h. Because moderate to severe exercise may significantly alter blood glucose concentration, it is not recommended during diagnostic testing, since in determining the etiology of brittle diabetes, as many variables as possible should be kept constant. All C-peptide–negative diabetic individuals can exhibit wide fluctuations in blood glucose concentrations with exercise.[28] There is extensive literature on the effects of moderate to severe exercise on glucose control, and this factor should be minimized during assessment of the brittle diabetic individual.[28] Another reason to establish the daily pattern of glucose control is to identify early morning hypoglycemia that leads to rebound hyperglycemia (Somogyi phenomenon). This response should be identifiable if blood glucose is measured at 3:00 a.m. during the week of glucose monitoring. In none of the brittle diabetic subjects referred to us was the Somogyi phenomenon responsible for diabetic instability, but other investigators have documented this etiology.[29]

(8) If the glucose response was appropriate when the nurse administered the insulin (i.e., a temporally related reduction in glucose concentration occurred), then the next step was to establish that the patient's injection technique was correct. This was accomplished by having the patient take responsibility for all insulin injections, and having experienced nurses observe his technique for 1 wk.

(9) If the patient responds appropriately to subcutaneous insulin injections, then he must be trained in the correct treatment of brittle diabetes, which consists of closely matching food intake and stress to the quantity and timing of insulin administered.[2–5,30,31] However, if it is evident that the patient is sufficiently knowledgeable about diabetes therapy and does not demonstrate wide fluctuations of blood glucose concentration under close observation, long-term follow-up in conjunction with the referring physician is necessary, as an intelligent patient who is malingering or has self-induced (factitious) disease will frequently not risk being caught. In our experience, the brittle diabetic individual with factitious disease will eventually reveal the cause of the brittleness by making an obvious mistake in therapy, if his physician is alert to this possibility.

(10) If the patient demonstrates glucose abnormalities (unexpected episodes of hypo- or hyperglycemia) when injecting the insulin himself, but normal glucose responses when a nurse injects the insulin, then factitious disease or malingering should be strongly considered, despite a "normal" health psychological evaluation. The establishment of factitious disease or malingering is extremely difficult and requires major effort on the part of the physician and health care team. Included in the evaluation of factitious disease is assaying the concentration of insulin in the bottle to exclude dilution of the insulin by the patient (as was done by one of our brittle patients). Furthermore, the patient's injection technique should be closely observed by a nurse to establish whether the patient is actually taking the insulin. Finally, it is most important that the family be interviewed to determine whether the patient has any reason to omit or otherwise alter his insulin injections, such as a school phobia, social interactive difficulties, or the need for increased attention.[32] Of the patients referred to us for evaluation, factitious disease and malin-

gering were the two most common etiologies (details of these patients are given in the companion article).[33] If no abnormalities are identified, step 7 is repeated to confirm that the patient's injection technique is the cause of brittle diabetes.

(11) If an abnormal glucose response occurs when the nurse injects the insulin, a subcutaneous dose response study should be performed to verify normal insulin absorption. This is done by giving the patient on separate days 0.1 U/kg and 0.5 U/kg insulin subcutaneously following withdrawal of maintenance intravenous insulin until glucose concentration reaches 250 mg/dl. With the 0.5-U/kg insulin dose, a significantly greater and more rapid decline in glucose concentration should be observed than when following the 0.1-U/kg insulin challenge dose in step 2.

(12) If an appropriate glucose response occurs to different challenge doses of insulin (which occurred in all of our subjects responding normally to the initial challenge dose of insulin [0.1 U/kg, step 2]), other causes of brittle diabetes must be considered. These include a significant delay in gastric emptying time (the etiology in two of our patients), which can be assessed by a Technetium-99, sulphur-colloid–containing meal.[7,34] If a significant delay is identified, then a trial of metoclopramide is warranted for diabetic gastroparesis.[35] Alternatively, it is possible that intermittent stress hormone excess is inducing the brittleness. Having excluded both acute and chronic disease (in step 1), the most common cause of stress hormone excess is emotional lability.[36] The health psychological evaluation should provide insight to this cause of brittle diabetes and consultation with a trained psychologist is required. Furthermore, during the week in which the subject is observed injecting his own insulin, emotional lability should be identifiable with a corresponding increase in blood glucose concentration. Family members are also helpful in providing insight to the patient's emotional status and metabolic decompensation. Two of our patients (both teenagers) had a history of the development of diabetic ketoacidosis coinciding with periods of emotional upset.

(13) If subcutaneous insulin injection results in an inappropriate glucose response to different doses of insulin, then repeat step 2, starting with the subcutaneous insulin dose. It is possible (although unlikely) that an abnormality in subcutaneous insulin absorption is cyclical and was not present on initial testing. We have never observed a change in glucose sensitivity sufficient to cause metabolic decompensation (although we have retested five patients to specifically exclude this possibility).

(14) If insulin challenge testing is abnormal, then efforts must be made to determine the site of insulin resistance. There are three principal locations at which insulin resistance can occur: (a) in the skin, (b) in the blood, and (c) at the peripheral tissue (cellular receptor or postreceptor level). If the abnormality is limited to the skin—that is, a subnormal glucose decline to subcutaneously injected insulin but a normal response to intravenously injected insulin—then a subcutaneous biopsy for insulin degrading activity is indicated.

(15) A subcutaneous skin biopsy is obtained under local anesthesia by the removal of 10 g tissue, which is immediately frozen for future assay. The specimen should be sent to a laboratory experienced in this determination.[37]

(16) If the subcutaneous tissue demonstrates excessive insulin degrading activity, alternative methods of insulin delivery should be considered, including additives to the insulin to increase absorption (xylocaine or Trasylol).[38,39] Alternatively, other insulin delivery routes should be explored (intravenous for short-term and intraperitoneal for long-term).[40] However, if the subcutaneous biopsy does not demonstrate increased insulin degrading activity, it is still possible that the absorption of insulin from the subcutaneous tissue is impaired by other mechanisms, such as subcutaneous fibrosis. In this case, alternative sites of insulin delivery should be considered (intravenous or intraperitoneal insulin delivery). However, of the 30 brittle diabetic subjects referred to us, we could not identify in any patient insulin resistance localized to the subcutaneous tissue. Because several referring physicians insisted that subcutaneous insulin resistance was the most likely etiology of their patients' brittle diabetes, we performed subcutaneous biopsies in seven patients. In no patient was increased insulin degrading activity present in the subcutaneous tissue or in the serum.

(17) If the blood glucose response to both intravenously and subcutaneously delivered insulin are abnormal, i.e., a decline of <95 mg/dl and 62 mg/dl by the subcutaneous and intravenous routes, respectively, then the site of resistance is either in the plasma or at the peripheral insulin target tissues. In this case, additional procedures are necessary to identify the defect.

(18) It is important to determine whether plasma free insulin levels demonstrate an appropriate rise following subcutaneous injection in step 2, since this provides direct evidence that the resistance is in the subcutaneous tissue. Thus, plasma for free insulin levels should be obtained during the insulin challenge testing.[41] The level of plasma free insulin determines the next step in the diagnosis.

(19) If the rise above baseline in plasma free insulin concentration is <5 μU/ml during 0.1 U/kg subcutaneous insulin challenge testing, then insulin degrading activity in serum should be measured, since it is possible that an insulinase is present in the plasma (or serum), reducing levels of free insulin.[42] If this is established, other insulin delivery routes (intravenous or intraperitoneal) should be considered in which high levels of free insulin can rapidly be achieved in the plasma so that the insulin may act before being degraded. However, all subjects demonstrated a rise of ≥5 μU/ml in free insulin concentration following the 0.1 U/kg subcutaneous insulin challenge test.

(20) An alternative explanation for relatively low plasma free insulin levels (5–10 μU/ml rise) following 0.1 U/kg insulin administered subcutaneously in the presence of high-affinity insulin antibodies that rapidly bind insulin, preventing (or delaying) its interaction with the cellular insulin receptor.[43,44] Insulin antibody titers were obtained commercially or from medical representatives from Eli Lilly and Company (Indianapolis, Indiana) or Squibb-Novo, Inc. (Clinton, Iowa). If high-titer antibodies are present, a trial of insulin

from a different species (e.g., human) is warranted, since it may be less antigenic than beef or pork insulin.[45] Alternatively, changing to U500 insulin has also been reported to be effective, but the mechanism is not resolved.[46]

(21) If the rise in plasma free insulin levels are normal during insulin challenge testing, then the defect is at the cellular level, i.e., either a decrease in insulin receptors, the presence of anti-insulin receptor antibodies (as exhibited by one of our patients),[47] or a cellular postinsulin receptor defect. These assays were obtained from either commercial or research laboratories.[8,48] These defects can sometimes be overcome by large doses of exogenous insulin. Since the injection of commercially available (100 U/ml) insulin may result in excessively large injection volumes, the use of more concentrated insulin is recommended.

CONCLUSION

The majority of the above procedures can be performed by the general practitioner who has access to subspecialty consultation. Several of the assays, however, require expertise available only in research laboratories. For each technique are given appropriate references, from which more details about the sample preparation can be obtained. From our experience with 30 brittle diabetic subjects, the etiology of diabetic instability can be correctly diagnosed in 97% (29 of 30) of cases, using the diagnostic algorithm shown in Figure 1. In the patient in whom we were unable to make a specific etiologic diagnosis, sufficient testing could not be completed because of poor patient cooperation and the occurrence of a "spontaneous remission" of the brittle diabetic state. In our experience, the success or failure of the treatment of brittle diabetes is dependent on therapy for the correct etiologic diagnosis, as detailed in the companion manuscript.[33]

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