Can Serum β-Hydroxybutyrate Be Used to Diagnose Diabetic Ketoacidosis?

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OBJECTIVE — Current criteria for the diagnosis of diabetic ketoacidosis (DKA) are limited by their nonspecificity (serum bicarbonate [HCO_3] and pH) and qualitative nature (the presence of ketonemia/ketonuria). The present study was undertaken to determine whether quantitative measurement of a ketone body anion could be used to diagnose DKA.

RESEARCH DESIGN AND METHODS — A retrospective review of records from hospitalized diabetic patients was undertaken to determine the concentration of serum β-hydroxybutyrate (βOHB) that corresponds to a HCO_3 level of 18 mEq/l, the threshold value for diagnosis in recently published consensus criteria. Simultaneous admission βOHB and HCO_3 values were recorded from 466 encounters, 129 in children and 337 in adults.

RESULTS — A HCO_3 level of 18 mEq/l corresponded with βOHB levels of 3.0 and 3.8 mmol/l in children and adults, respectively. With the use of these threshold βOHB values to define DKA, there was substantial discordance (~≥20%) between βOHB and conventional diagnostic criteria using HCO_3, pH, and glucose. In patients with DKA, there was no correlation between HCO_3 and glucose levels on admission and a significant but weak correlation between βOHB and glucose levels ($P < 0.001$).

CONCLUSIONS — Where available, serum βOHB levels ≥3.0 and ≥3.8 mmol/l in children and adults, respectively, in the presence of uncontrolled diabetes can be used to diagnose DKA and may be superior to the serum HCO_3 level for that purpose. The marked variability in the relationship between βOHB and HCO_3 is probably due to the presence of other acid-base disturbances, especially hyperchloremic, nonanion gap acidosis.

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Recently published consensus criteria for diagnosing diabetic ketoacidosis (DKA) include a serum bicarbonate (HCO_3) level ≤18 mEq/l, pH ≤7.30, the presence of ketonuria/ketonemia, an anion gap >10 mEq/l, and a plasma glucose concentration >250 mg/dl (13.9 mmol/l) (1). The development of a consensus statement represents an advance in view of the divergence of opinion that has existed concerning what the standards for diagnosis of DKA should be (2). However, these diagnostic criteria have limitations. Anion gap, HCO_3, and pH are relatively nonspecific for DKA because they can be affected by the degree of respiratory compensation or the presence of a separate acid-base disturbance. Ketonuria and ketonemia are usually determined with the nitroprusside assay, which detects acetoacetate (AcAc) but not the most abundant ketone body, β-hydroxybutyrate (βOHB) (3). Moreover, the measurement is not quantitative (4).

Ketone body anion concentrations (i.e., AcAc and βOHB), on the other hand, directly reflect the rate of ketone body production (5), which is accompanied by equimolar production of hydrogen ions (6). The present study was undertaken to investigate how a laboratory-based measurement of serum βOHB might be used as part of simplified diagnostic criteria for the diagnosis of DKA.

RESEARCH DESIGN AND METHODS

We retrieved electronic medical records data from Mayo Clinic Rochester patients from January 1994 through October 2006 according to a protocol approved by the Mayo Institutional Review Board. The data were retrieved by ICD-9 codes (250.12 and 250.13) and for simultaneous measurements of βOHB and HCO_3. A total of 545 encounters were initially identified. Age, type of diabetes (1 or 2), and admission blood tests, including measurements of glucose, βOHB, HCO_3, pH, and lactate were recorded if available. Serum βOHB was measured on the P Module of a Roche Modular Analytics system, using reagent provided by Roche Diagnostics (Indianapolis, IN). The coefficient of variation ranged from 4% (at levels of 1 mmol/l) to < 1.5% (at levels >4 mmol/l).

The discharge summary or admission note was used to determine type of diabetes. In each encounter, the temporal relationship between blood tests and initiation of insulin therapy was noted. Encounters in which serum glucose, βOHB, or HCO_3 were either not available at all or were obtained after initiation of therapy were excluded. βOHB and HCO_3 were compared using regression analysis to determine the βOHB value that corresponded with a serum HCO_3 level of 18 mEq/l. Using that βOHB value to define DKA, data were then analyzed to assess the degree of diagnostic discordance between βOHB and HCO_3. βOHB values corresponding to HCO_3 levels of 15 and 10 mEq/l, values used to define moderate and severe DKA, respectively (1), were also determined by regression analysis.

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Abbreviations: AcAc, acetoacetate; βOHB, β-hydroxybutyrate; DKA, diabetic ketoacidosis; HCO_3, bicarbonate; HHS, hyperglycemic hyperosmolar syndrome; POC, point-of-care; ROC, receiver operating characteristic.

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Because of known differences in buffering capacity related to age (7), data from children (<16 years of age) and adults (≥16 years of age) were analyzed separately as well as in aggregate. Sensitivity and specificity for serum HCO_3 values were addressed through receiver operating characteristic (ROC) analysis (8). The area under the ROC curve summarizes the accuracy of classification. Data are expressed as means ± SEM.

RESULTS — A total of 466 encounters in 304 patients met the inclusion criteria for the study and were analyzed. Twenty-eight percent of the encounters occurred in patients aged <16 years. The mean ages of the children and adults were 10.8 ± 0.4 and 33.2 ± 1.1 years, respectively. In 99 of the episodes, the hospitalization was the occasion for a new diagnosis of diabetes.

The relationship between HCO_3 and βOHB was curvilinear, and the best fit was obtained with a polynomial regression in each instance. When children and adults were analyzed separately, the βOHB values that corresponded with a HCO_3 value of 18 mEq/l were 3.0 and 3.8 mmol/l, respectively, with a strong negative association (Fig. 1). The corresponding βOHB values for a HCO_3 level of 15 mEq/l were 4.4 and 5.1 mmol/l, whereas the corresponding βOHB values for a HCO_3 level of 10 mEq/l were 7.7 and 8.9 mmol/l, respectively.

Using βOHB values ≥3.0 mmol/l in children and ≥3.8 mmol/l in adults to define DKA, 248 episodes of DKA in 200 patients were identified. There were 218 encounters in 147 patients with lower βOHB values (<3.0 mmol/l in children and <3.8 mmol/l in adults) (without DKA). Table 1 shows the frequency of type 2 diabetes, together with concentrations of βOHB, HCO_3, glucose, pH, and lactate in patients with and without DKA thus defined. As can be seen, pH and lactate data were available for only a minority (~28%) of patients. Among those who had lactate measured, lactate was >4 mmol/l in ~12% of encounters (n = 7 each among patients with and without DKA).

The admission glucose concentration was ≤13.9 mmol/l in ~8% of both children and adults with DKA. The pH was >7.30 in 7% of children and 20% of adults with DKA and ≤7.30 in 25% of children and 11% of adults without DKA. The HCO_3 level was >18 mEq/l in 7% of children and 17% of adults with DKA, whereas it was ≤18 mEq/l in 14% of children and 16% of adults without DKA. There was diagnostic discordance between the βOHB cutoff and at least one of the conventional diagnostic criteria (HCO_3, pH, or glucose) in 15% of children and 27% of adults with DKA. Table 2 shows the sensitivity and specificity of serum HCO_3 when it was used to diagnose DKA defined by the βOHB criteria, based on ROC analysis. The areas under the ROC were 0.953 and 0.909 in children and adults, respectively.

The relationship between glucose level and acidosis in DKA encounters was examined by regression analysis, using both HCO_3 and βOHB as an index of severity of acidosis. Because the analysis showed no difference between children and adults, the results were combined. There was no correlation between HCO_3 and glucose (Fig. 2, *upper panel*). In contrast, there was a significant correlation between βOHB and glucose, although it was rather weak (Fig. 2, *lower panel*). These latter two observations were essentially identical when DKA was defined by HCO_3 instead of by βOHB (not shown). Glucose concentrations were 26.4 ± 0.8 and 23.9 ± 1.4 mmol/l in patients with HCO_3 levels of ≤15 and 16–18 mEq/l, respectively (NS). Glucose levels were

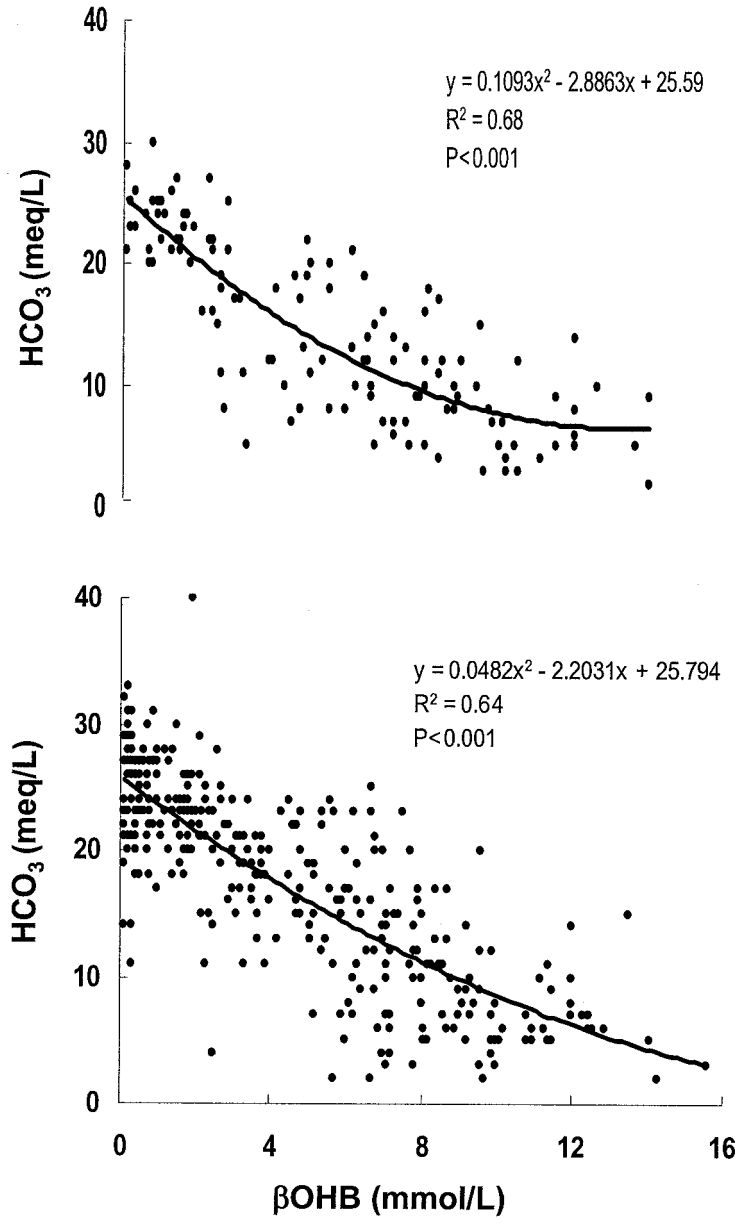

Figure 1— *Relationship between serum HCO_3 and βOHB in hospitalized children* (upper panel) *and adults* (lower panel) *with diabetes.*

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>33.3 mmol/l in 23 and 17% of patients in the two groups (not shown).

CONCLUSIONS — The results of the present study demonstrate that in hospitalized patients with diabetes, a serum HCO_3 level of 18 mEq/l corresponds with serum βOHB levels of 3.0 mmol/l in children and 3.8 mmol/l in adults. They also indicate that when these βOHB levels are used for the diagnosis of DKA, there is discordance with conventional criteria.

In the past, a variety of diagnostic criteria have been used for DKA, including total ketone body anion (AcAc + βOHB) concentrations of 3 mmol/l (9) or 5 mmol/l (10), pH values <7.37 (11) or <7.20 (12), and serum HCO_3 levels of 18 mEq/l (13) or 15 mEq/l (14). Considering this divergence of opinion, the recently published consensus criteria (1) are a positive development. However, the criteria have limitations. Whereas confirmation of ketonemia/ketonuria may be diagnostically useful in the absence of a ketone body anion measurement such as βOHB, it provides only subjective, qualitative information (4). In a position statement that is somewhat contradictory to the consensus criteria, the American Diabetes Association stated that urine ketone tests are not reliable for diagnosing DKA and that measurement of βOHB in blood is preferred, although no mention was made of specific βOHB levels (15).

Perhaps the most widely used test for defining DKA, at least in research studies, has been the serum HCO_3 value. The HCO_3 value has the advantage of being less susceptible than pH to abrupt changes in ventilation, but like pH it is nonspecific. Baseline HCO_3 values before the onset of DKA may vary because of preexisting acid-base disturbances, including chronic renal disease with acidosis (low baseline HCO_3 value) and chronic respiratory acidosis (high baseline HCO_3 value). Acute disturbances can also contribute to changes in HCO_3 levels. Nausea and vomiting are common in patients who present with DKA and can result in metabolic alkalosis consequent to loss of $[H^+]$ (16). An acute accumulation of other organic anions such as lactate can also contribute to changes in HCO_3 values. The variability in the relationship between βOHB and HCO_3 values found in the present study is consistent with contributions from all of these factors.

AcAc, as an unmeasured anion that is increased in DKA, is a potential contributor to this variability. The average βOHB-to-AcAc ratio in DKA has been reported to be 3.0:1 to 3.2:1 (17,18). However, there have been case reports of "nitroprusside-negative" patients with ratios >7:1 (3). In a review of the literature, we found seven studies in which individual βOHB and AcAc concentrations were available in 61 patients with DKA. In these seven studies, the mean βOHB-to-AcAc ratio was 3.0:1 with a coefficient of variation of 30% (see details in the online appendix available at http://dx.doi.org/10.2337/dc07-1683). This finding suggests that differences in AcAc concentrations contribute little to the observed variability in the relationship between βOHB and HCO_3 levels in the present study and that factors such as concurrent lactic acidosis (19) and especially hyperchloremic nonanion gap acidosis (20) are more likely to be responsible.

Previous studies have shown that children have lower extracellular buffering capacity than adults (7). It is unclear whether this is due to chronic respiratory alkalosis, an acidification defect due to renal immaturity, or perhaps other factors. Nonetheless, our findings indicate that for a given degree of hyperketonemia in DKA, children can be expected to have more severe acidemia than adults. For this reason, it seems appropriate to apply a different diagnostic standard for DKA in

Table 1—*Clinical and laboratory data in hospitalized diabetic patients with and without ketoacidosis*

	Children (n = 129)		Adults (n = 337)		Total (n = 466)	
	Without DKA (βOHB <3.0 mmol/l)	With DKA (βOHB ≥3.0 mmol/l)	Without DKA (βOHB <3.8 mmol/l)	With DKA (βOHB ≥3.8 mmol/l)	Without DKA	With DKA
n	43	86	175	162	218	248
Type 2 diabetes	0 (0)	0 (0)	32 (19)	14 (8)	31 (14)	15 (6)
βOHB (mmol/l)	1.5 ± 0.1	7.7 ± 0.3*	1.4 ± 0.1	7.7 ± 0.2*	1.4 ± 0.1	7.7 ± 0.2*
HCO_3 (mEq/l)	22 ± 0.6	10.4 ± 0.5*†	22.8 ± 0.4	12.0 ± 0.5*	22.7 ± 0.3	11.5 ± 0.4*
Glucose (mmol/l)	19.1 ± 1.5	28.0 ± 1.4*	19.9 ± 0.9	25.7 ± 0.9	19.5 ± 0.7	26.6 ± 0.7*
pH	7.34 ± 0.02 (4)	7.17 ± 0.01 (27)	7.41 ± 0.01 (35)	7.18 ± 0.01 (69)*	7.40 ± 0.01 (39)	7.18 ± 0.01 (96)*
Lactate (mmol/l)	2.36 ± 0.21 (9)	1.61 ± 0.10 (15)	2.02 ± 0.10 (59)	2.38 ± 0.11 (49)	2.05 ± 0.09 (68)	2.21 ± 0.08 (64)

Data are n (%), means ± SD, or means ± SD (n). *P < 0.001 vs. patients without DKA; †P = 0.028 vs. adults.

Table 2—*Sensitivity and specificity of serum HCO_3 in diagnosing DKA defined by βOHB (≥3.0 mmol/l in children, ≥3.8 mmol/l in adults), using ROC analysis*

	HCO_3^- (mEq/l)	Sensitivity (%)	Specificity (%)
Children	21	98.8	60.5
	18	91.9	86.0
	15	81.4	93.0
	10	57.0	97.7
Adults	21	91.3	62.6
	18	82.6	83.9
	15	70.2	92.5
	10	44.1	99.4

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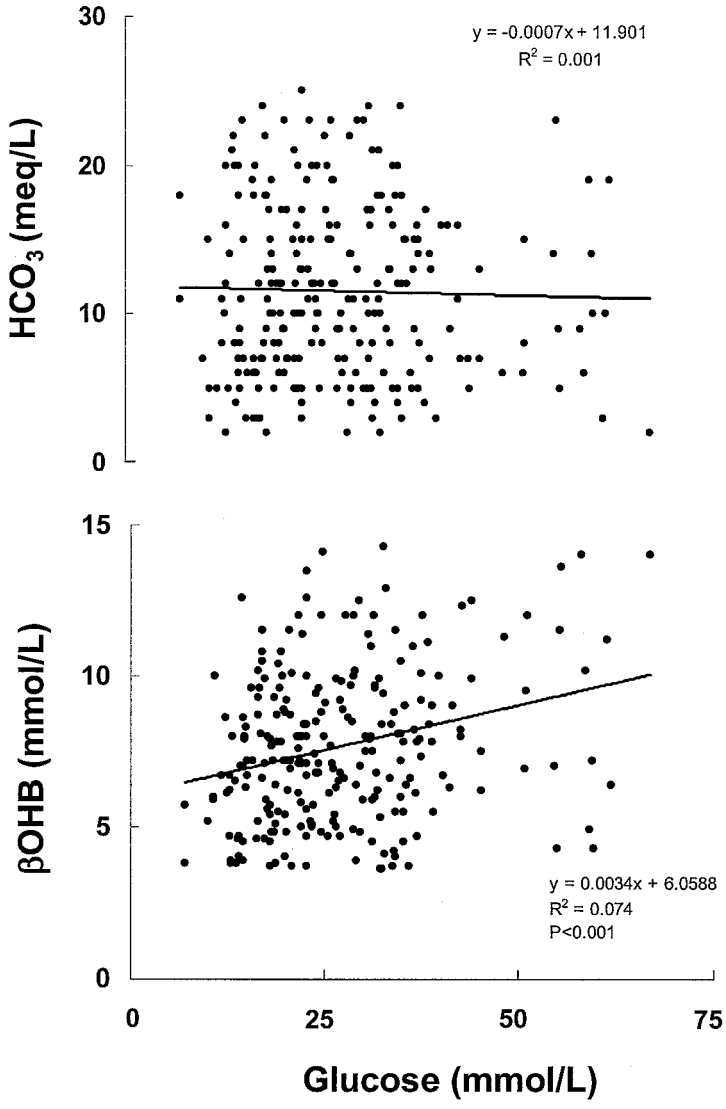

Figure 2— *Relationship between serum HCO_3 and glucose* (upper panel) *and serum βOHB and glucose* (lower panel) *in adults and children with DKA.*

children than in adults. In fact, a lower total ketone body anion concentration (3 mmol/l) has been suggested for a diagnosis of DKA in children (9) than that proposed for adults (5 mmol/l) (10).

The fact that nonspecific tests of acid-base status such as pH and HCO_3 are central to the diagnosis of DKA may relate to their availability. For many years, βOHB was a research test that was not practical for clinical use. However, the widespread use of open-channel automated chemistry analyzers (21) makes it possible for virtually any laboratory to perform tests for βOHB levels rapidly.

Point-of-care (POC) βOHB testing has recently received increased attention, but the procedure has limited precision above concentration of 2.5–3.0 mmol/l (22). For this reason, we believe that POC methods can be useful for self-monitoring (and possibly the prevention of DKA), but that a laboratory-based test would be preferable for diagnostic purposes until a POC method with improved precision and accuracy is available. Other investigators and the World Health Organization have taken a similar position on POC glucose testing (23).

A limitation of our study is that it is retrospective. Furthermore, it does not provide actual proof that βOHB is superior to HCO_3 for the diagnosis of DKA. Rather, such a conclusion must be arrived at on theoretical grounds. Fulop et al. (21) compared βOHB to both serum CO_2 content and anion gap in 64 DKA encounters and concluded that the correlations were too weak for βOHB to be useful to assess the severity of ketoacidosis. This conclusion is based on the assumption that HCO_3 is the "gold standard" for diagnosing DKA, however. If βOHB were the gold standard, imperfections in the relationship between βOHB and measures of metabolic acidosis such as HCO_3 (whether βOHB explains 36% of the variability in HCO_3 as Fulop et al. reported or ~64% as we found) would only attest to the nonspecificity of HCO_3 for DKA. Adrogue et al. (20) reported that half or more of patients presenting with DKA had a significant hyperchloremic, nonanion gap acidosis attributable to renal loss of potential HCO_3 in the form of ketonuria, separate from the anion gap acidosis resulting from overproduction and accumulation of ketone bodies (20). This indicates that a process other than ketoacidosis contributes to depression of serum HCO_3 in patients with DKA and may be a major contributor to the diagnostic discordance between βOHB and HCO_3 that we observed. Moreover, there is no evidence to suggest that hyperchloremic acidosis contributes to morbidity and mortality in DKA; in fact, patients with DKA and hyperchloremic acidosis have less dehydration and therefore presumably less hyperosmolality, conditions that are both thought to contribute to mortality (12,24), than individuals with "pure" ketoacidosis (20).

We found that when lactate concentrations were measured in patients with DKA, they were >4 mmol/l in ~12% of patients. Lactic acidosis has been defined as a lactate concentration ≥4 mmol/l (25) or ≥5 mmol/l (26); using the latter definition, Nattrass and Alberti (19) found lactic acidosis in 15% of patients with DKA. Because of this finding and because elevated lactate concentrations appear to portend a poor prognosis (27), we believe measurement of lactate should be performed routinely on admission in patients with DKA.

In the present study, there was no correlation between HCO_3 and glucose in patients with DKA as reported previously (2), a further reflection of the nonspecificity of HCO_3 for DKA. In contrast, there was a significant but quite weak correlation between βOHB and glucose. The weakness of the correlation is consistent with uncoupling between hepatic production of ketone bodies and glucose. It has been known for many years that hyperglycemia may be surprisingly mild in DKA (28), and glucose production rates can be near normal (29); the therapeutic implications of this are obvious and have

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been discussed (2). We also found no difference in the severity of hyperglycemia or incidence of hyperosmolarity (glucose concentration >13.3 mmol/l) in patients with mild DKA (HCO_3 level of 16–18 mEq/l) (1) and patients with moderate or severe DKA (HCO_3 level of <16 mEq/l). This result indicates that the concept of a finite overlap between DKA and hyperglycemic hyperosmolar syndrome (HHS) (defined as a glucose concentration of >13.3 mmol/l and including patients with HCO_3 levels in the 16–18 mEq/l range) (1) may be somewhat artificial, because patients with DKA with and without HHS are equally hyperglycemic. In other words, DKA can present with or without hyperosmolality irrespective of the severity of acidosis, and HHS can present with or without DKA.

In summary, we suggest that DKA can be defined as uncontrolled diabetes accompanied by a βOHB level ≥3.0 mmol/l in children and ≥3.8 mmol/l in adults. Certainly, any diagnostic criterion for DKA is arbitrary. We do not suggest that patients with levels below such an arbitrary cut point for diagnosis would automatically be managed differently than those with levels above it. The use of such a cut point does not supersede clinical judgment, but it does in our view impose additional, and desirable, diagnostic rigor. The minimum βOHB concentration that we suggest be present for a diagnosis of DKA in adult patients (3.8 mmol/l) not only relates to a serum HCO_3 level of 18 mEq/l but also, assuming a βOHB-to-AcAc ratio of 3.0:1 (see above), corresponds almost exactly to the 5 mmol/l total ketone body anion concentration threshold suggested by Alberti and Hockaday (10). This definition of DKA is more precise and quantitative than previous criteria for a diagnosis of DKA. However, it is not practical to make the βOHB test available with a rapid turnaround unless a hospital has a relatively large volume of patients with DKA. Further evaluation of its use in prospective studies, in combination with other diagnostic criteria, is needed.

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