preferable to measurement of free T₃ in screening for hypothyroidism.

References

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Delayed Activity of γ-Glutamyltransferase in a Patient with Cryoglobulinemia and the Hyperviscosity Syndrome

To the Editor:

Measurement of γ-glutamyltransferase (EC 2.3.2.2) is useful clinically in helping to diagnose certain types of liver disease (1). Values are highest in obstructive jaundice and moderately high in alcoholics, especially those with previous liver damage and recent ingestion of alcohol, and in patients on long-term anticonvulsant therapy. Depressed values are unusual. Jaundice is thought to cause low values, by some unknown mechanism (2). A deficiency of this enzyme has also been described (3). We describe here a case of delayed activity of γ-glutamyltransferase in a patient with cryoglobulinemia and the hyperviscosity syndrome.

The patient, a 57-year-old woman, had been diagnosed 10 months earlier as having chronic lymphatic leukemia. She was treated with chlorambucil and the disease was in remission. When seen in the present occasion she presented with dizziness, loss of hearing, tinnitus, and fainting spells. A tentative diagnosis of Ménière’s disease was made.

In the laboratory, the serum was noted to be extremely viscous. The hemoglobin concentration was 8.5 g/L, the hematocrit 25%, and the leukocyte count 8.2 × 10⁹/L with 78% lymphocytes and 22% neutrophils. Values for serum urea, creatinine, and electrolytes were normal. Other values were: calcium 2.21 mmol/L, uric acid 0.46 mmol/L, total bilirubin 4 μmol/L, alka-line phosphatase 32 U/L, γ-glutamyltransferase (no value obtainable, discussed later), aspartate aminotransferase 240 U/L, total protein 84 g/L, albumin 32 g/L, and globulin 52 g/L. The relative viscosity of the serum at 37 °C was 18.9.

The test for cryoglobulin was positive. The cryoprecipitate was separated by leaving the serum overnight in the refrigerator at 4 °C, then centrifuging. The supernate showed the following: total protein 60 g/L, albumin 42 g/L, total globulin 18 g/L, alkaline phosphatase 45 U/L, y-glutamyltransferase 30 U/L, and aspartate aminotransferase 29 U/L. The abnormal protein was identified by immunofixation as an IgM. The light chain was not characterized.

The γ-glutamyltransferase activity was determined by the method of Szasz (4) in a centrifugal analyzer (GEMSAEC; Electro-Nucleonics, Fairfield, NJ 07006) with “Spin Chem” reagents from SmithKline Instruments, Sunnyvale, CA 94086. The relevant settings used were initial reading 30 s, reading interval 30 s, number of readings 5, temperature 30 °C. The printout of the assay of this enzyme showed an apparent high value for this patient. However, the Multiple Data Printout showed a continuous decline in the absorbance. To determine the reasons for this, we repeated the test, monitoring the absorbance at 1-min intervals for 15 min. The result is shown in Figure 1, curve 4: an initial high absorbance, followed by a rapid decline for about 3 min, and then a gradual linear rise. Under normal circumstances the first reading is taken about 1 min after the reaction is begun. At this time the absorbance was still being measured, which accounted for the spurious results originally obtained. If the linear part of the curve had been used to measure the activity, it would have been about 27 U/L.

Other enzymes that were determined (alkaline phosphatase, aspartate aminotransferase, creatine kinase, and α-hydroxybutyrate dehydrogenase) did not give this problem. Figure 1, curve 3 shows the absorbance change for alkaline phosphatase at the identical instrumental settings. Here the initial absorbance is also high but at 1 min the linear phase of the reaction had already begun. When 9 g/L sodium chloride solution (Figure 1, curve 6) was used as “reagent,” there was also a gradual decrease in absorbance, similar to that seen for γ-glutamyltransferase. In contrast, a pooled serum showed linear reactions (Figure 1, curves 1, 2, and 7), beginning even at the “early reading” phase, about 10 s after the start of the reaction.

Two factors probably contribute to the delayed activity of γ-glutamyltransferase: the cryoglobulin and the hyperviscosity. This is supported by the fact that removal of the cryoprecipitate resulted in a normal curve for the activity of the resulting supernatant fluid (Figure 2, curve 3). Hyperviscosity probably plays a minor part, because the problems persisted with other samples from this patient, even those with a relative viscosity as low as 8 and diluted as much as 10-fold. The serum itself appeared cloudy at room temperature, but this was not the result of hyperlipidemia (cholesterol 2.3 mmol/L, triglycerides 0.73 mmol/L). Probably the cryoglobulin was precipitating at room temperature. Figure 2 shows the absorbance changes occurring when the cryoprecipitate was mixed with sodium chloride at room temperature and its apparent "activity" determined. As can be seen (Figure 2, curves 3, 4, and 5), curves similar to those seen with the original serum were obtained.

The reason why only γ-glutamyltransferase activity is affected under normal circumstances is not clear. The only difference between the reagent used and the others purchased from SmithKline is that it must be placed in a water bath at 37 °C for a few minutes for it to be dissolved.
Routine Screening for Prostatic Cancer by Assay of Serum Acid Phosphatase: A Modest Proposal

To the Editor:

Carcinoma of the prostate is prevalent in elderly men (1, 2), but is curable with early diagnosis (2). Sensitive assays for prostate acid phosphatase (EC 3.1.3.2; PAP) were initially viewed as a means to achieve early diagnosis through routine screening (3, 4). The enthusiasm for routine screening waned, however, when assay of PAP in serum was demonstrated to possess only moderate predictive value for carcinoma (5–7). Some urologists now believe the traditional digital rectal examination is superior to PAP as a diagnostic test (8).

It is important to realize that the evaluations of PAP and the comparisons between PAP and rectal examination were based on arbitrary boundaries between positive and negative values based on inter-individual reference ranges. While these criteria are satisfactory for evaluation of the subjective and qualitative digital rectal examination, they are far from optimal for the objective and quantitative PAP test (9–11). Before dismissing routine screening with PAP as unreliable, we should evaluate the advantages of the intra-individual reference ranges that would result from routine screening (12, 13). Rather than asking if a given test were positive or negative, we could scrutinize the variation in PAP with advancing age for each individual and describe the shape of a curve for normal PAP vs age. Then, if routine screening was initiated in middle age when the prevalence of prostatic carcinoma is small (1), any unusual change in the shape of the curve for PAP vs age in any individual would be outstanding. The background data for that individual would permit ready confirmation of abnormality on repeat testing. The potential to substantially improve the reliability of PAP by means of intra-individual reference ranges would seem to warrant a trial, e.g., annual screening in a cohort of middle-aged men.

References

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Table 1. Serum 1,5-Anhydroglucitol (AG) and Blood HbA1c Concentration (Range and Mean) in Type 1 (Insulin-Dependent) Diabetics during Continuous Insulin Infusion

<table>
<thead>
<tr>
<th>Serum 1,5-Anhydroglucitol</th>
<th>Blood HbA1c, %</th>
<th>Clinical nephropathy failure</th>
<th>No clinical nephropathy failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration in Diabetic Patients</td>
<td>Receiving a Continuous Subcutaneous Infusion of Insulin</td>
<td>(n = 7)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>0–6.8</td>
<td>6.0–4.6</td>
<td>1–4.2</td>
<td>(3.2)</td>
</tr>
<tr>
<td>6.9–10.2</td>
<td>4.7–3.2</td>
<td>(2.4)</td>
<td>(3.2)</td>
</tr>
</tbody>
</table>

*Upper normal limit, 8.5%