Pathology Feature

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Sequential investigation of aspartate aminotransferase elevation in outpatients[1]

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The authors used a computer-based protocol to evaluate the significance of elevations in aspartate aminotransferase (AST) activity in outpatients undergoing periodic health examinations. The protocol was used to systematically guide the performance of confirming secondary tests when the initial AST activity was elevated. Interpretation of all laboratory results was computer generated by an EXPERT artificial intelligence program developed by the authors. Implementing this system in a laboratory-based accelerated testing program resulted in the investigation of 79 AST elevations in 3,096 outpatients; 93% of these results were confirmed by secondary testing and represented apparent alcohol-induced liver dysfunction, hepatitis (including HBV), unclassified liver dysfunction, muscle insult, or hypothyroidism. This laboratory testing protocol appears to be an attractive alternative to traditional laboratory screening.

Index terms: Decision making, computer-assisted · Pathology features

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Elevations of serum aspartate aminotransferase (AST) activity are not rare in the outpatient setting when obtained as part of a biochemical profile. The utility of multiphasic laboratory testing has been debated for several years. The low prevalence of disease (and its association with low test predictive value), lack of physician response to reported abnormalities, and cost have been cited as major disadvantages of laboratory screening.[1–3] Others have argued that cost has been overestimated, that the available knowledge base has not been exploited.[4–6] There is evidence that many unexpected laboratory abnormalities are not investigated

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See also the editorial by Berger-Hershkowitz and Neuhauser (pp 165–166).

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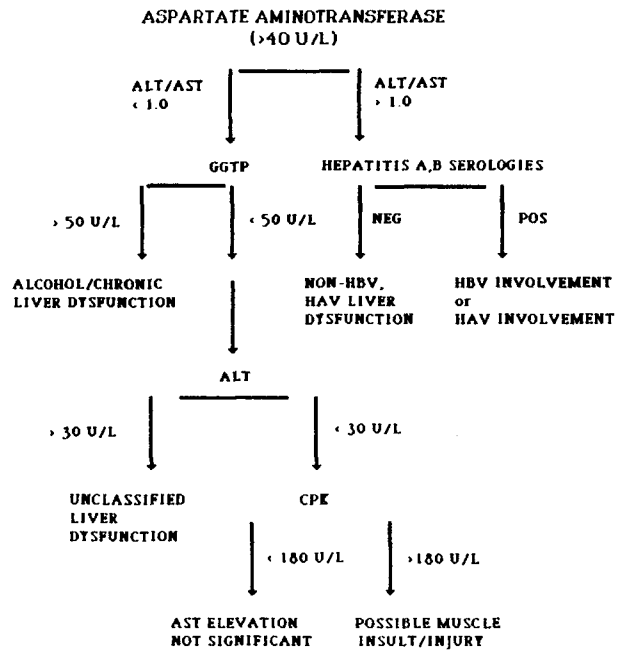

Fig. Algorithm used for sequential laboratory investigation and interpretation of initial AST elevations.

during the course of patient evaluation.[7] Laboratory-directed sequential investigation of initial test abnormalities has been advocated as a means to increase information yield. Altshuler and associates[8,9] developed such a system—Programmed Accelerated Laboratory Investigation (PALI)—which involved sequential testing performed by the laboratory automatically without requiring additional physician orders.

We have developed a similar sequential laboratory investigation protocol for automatic, secondary testing to both confirm an initial AST elevation and provide an interpretation of results. The secondary test results are used to assess the presence of conditions most likely to be the cause of AST elevations at the time of routine health examinations (alcohol-related liver changes, viral hepatitis, or muscle insult). In addition, nonspecific liver dysfunction and clinically insignificant AST changes can be detected. This approach is implemented using an EXPERT artificial intelligence program that both directs secondary testing and renders a final computer-generated interpretation. We report here a study of the incidence of AST elevations in 3,096 outpatients seen for routine health examination and our experience with a computer-directed laboratory investigation of these abnormalities.

Materials and methods

The study included 3,096 patients (2,827 men [age range, 17–83 years] and 269 women [age range, 18–70 years]) seen for routine periodic health examinations as part of an executive health program. The volume of blood drawn was sufficient for obtaining a biochemical profile, a complete blood count (CBC), and possible secondary testing. A completed clinical history questionnaire, submitted to the laboratory as part of the requisition for sequential laboratory investigation, established the presence or absence of a history of diabetes, hypothyroidism, and jaundice and indicated the patient's medication and ethanol intake.

The biochemical profile, performed with an SMA-II analyzer (Technicon Instruments Corp.), consisted of total protein, calcium, phosphorus, total bilirubin, uric acid, aspartate aminotransferase (AST, EC 2.6.1.1), lactate dehydrogenase (LD, EC 1.1.1.27), alkaline phosphatase (AP, EC 3.1.3.1) and glucose. CBC was determined with an S-Plus IV analyzer (Coulter Electronics Inc.). All secondary tests were performed using typical procedures.

The computer program was developed with the EXPERT consultation system provided by the Department of Computer Sciences at Rutgers University.[10,11] Software was programmed on a VAX 730 computer (Digital Equipment Co.) with the VAX/VMS 4.1 operating system. EXPERT computer programs are designed to mimic the logic process of a human "expert." They are implemented by incorporating the knowledge base and problem-solving approach of the expert. The EXPERT model development system is composed of three sections. The Taxonomy section contains conclusions which may be inferred by the program (in this case, secondary test requests and interpretative comments). The Findings section contains patient-specific data, including results of screening tests, clinical history, and secondary tests that may be required by the program. The Rules section contains decision rules that relate findings and conclusions. The conclusions may be either requests for additional tests or interpretations of a completed investigation.

The decision rules are represented by an algorithm (*Figure*) which is designed to evaluate the possible presence of viral hepatitis, alcohol-induced liver dysfunction, muscle insult, or unclassified liver dysfunction. This algorithm was based on laboratory testing strategies currently ac-

cepted by the authors as appropriate for differentiating the pathologies that may cause AST elevations in outpatients and represent generally accepted laboratory investigation.[12,13] This approach is designed to reduce the diagnostic possibilities, not to force an unequivocal diagnosis for all patients, by maximizing the specificity of the acquired laboratory data.

The alanine aminotransferase (ALT)/AST ratio is requested for all patients with AST >40 U/L.[14] For patients exhibiting ratios of 1 or greater, hepatitis A and hepatitis B serology testing for evidence of viral hepatitis infection is requested. When patients have ratios less than 1, gamma-glutamyl transferase (GGT) activities are requested to assess the presence of ethanol-related liver dysfunction. If neither ALT and GGT activities exceed their reference intervals, the possibility of muscle insult or injury is investigated and the program requests total creatine kinase (CK,EC 2.7.3.2) and CK isoenzyme activities.

The EXPERT program is designed to evaluate test results on all patients and performs a sequential laboratory investigation whenever the initial AST result is abnormal. If the initial AST result exceeds 40 U/L, the computer will ask for supplemental testing required by the program for evaluation. The program requests only the additional testing required for each case and will not attempt interpretations until all necessary data are obtained. As each requested test result is entered, the program evaluates all available findings and rules and asks for unknown, required information. Following the scheme shown in the *Figure*, the model progresses in a sequential fashion until all required supplemental testing is completed and the results interpreted or the patient cannot be classified.

Medical charts were reviewed retrospectively for physical-examination and ancillary-test findings (e.g., ECG results and chest radiographs, past medical history, examination conclusions, and patient follow-up). This was done in order to assess any clinical findings that could signal a condition implied by the laboratory data. Comparison of data groups was accomplished using the *t* test.

Results

Seventy-nine of 3,096 patients evaluated (2.55%) exhibited AST activity greater than 40 U/L (the upper limit of the reference interval). Values ranged from 41 to 205 U/L (mean, 59.6 U/L [SD = 24.2 U/L]). The reference interval limit had been previously set to include greater than 99% of a referent normal population. Of these patients, 11 had exhibited previous AST elevations within the previous two years. The remaining 3,017 patients exhibited a significantly lower mean AST activity of 19.7 U/L ($P < 0.01$, $t = 50.42$). The patients with elevated AST activity also demonstrated significantly higher ($P < 0.01$) mean concentrations of glucose, uric acid and AP, as well as a higher mean corpuscular volume than those without elevated AST.

Table 1 lists the degree of abnormality observed in both secondary test results performed according to the computer algorithm and concurrent liver function tests present in the initial biochemical profile. Of the 79 patients with AST elevations, 63 represented the only abnormality on the biochemical profile, while 16 had other abnormal test results including either increased total bilirubin concentrations, AP activities, or LD activities. Only 4 of these patients exhibited liver-related findings on physical examination.

Table 1. Abnormalities shown by associated screening and secondary tests of patients with elevations of AST activity

Test	No. of patients	No. abnormal (%)
Alanine aminotransferase*	79	65 (82.3)
Gamma glutamyl transferase*	79	45 (57.0)
Hepatitis serologies*	44	5 (11.4)
Creatine kinase*	10	6 (60.0)
Total bilirubin†	79	7 (8.9)
Alkaline phosphatase†	79	3 (3.8)
Lactate dehydrogenase†	79	9 (11.4)

* Secondary test performed due to initial AST elevation.
† Concurrent biochemical profile test.

Table 2. EXPERT computer interpretations reported on 79 outpatients with initial elevations of AST activity

Interpretation	No. of cases	% of cases	% of total population
Non HBV, HAV liver dysfunction	42	53.2	1.3
Muscle insult/injury	9	11.4	0.2
Alcohol-induced	15	19.0	0.5
Hepatitis B	5	6.3	0.2
Nonspecific liver dysfunction	3	3.8	0.1
Not classified	5	6.3	0.2

Confirmation of the initial AST elevation by subsequent test abnormalities in either ALT, GGT, or CK was made in 74 of 79 cases. This finding is significant and further supports the notion that an elevation of AST in this population represents some degree of biochemical pathology, rather than a purely statistical effect.

The computer-derived classification of these patients according to possible conditions present is shown (*Table 2*). The most frequent finding of liver dysfunction associated with negative HAV, HBV serologies derives from confirmation of an AST elevation by subsequent determination of an elevated ALT activity of greater magnitude but negative hepatitis A, B serologies (45 patients). This classification is not equivalent to what is now referred to as non-A, non-B hepatitis, which requires a more specific and defined clinical history. Twenty-six of these patients also had elevated GGT activity. Three of these 45 patients also exhibited elevated LDH activities, 1 had an elevated AP level, and only 1 had hyperbilirubinemia. With the exception of 1 patient who reported a past history of jaundice, there were no additional indications for a more specific cause of liver dysfunction in these patients, although 2 exhibited hepatomegaly on physical examination. Five of these patients had previous elevations in AST activity. To date we have not extended the laboratory investigation of patients with this spectrum of findings, although alcohol/drug-related changes, for example, may be present and prior history of blood transfusions could signal non-A, B viral hepatitis exposure. Three patients in this group presented for repeat testing following a four-week abstinence from alcohol and all exhibited AST activities within the reference interval.

Fifteen patients were classified as possibly having an alcohol-related liver dysfunction; of these, 12 presented with a history of alcoholism or heavy drinking (>4 oz daily), although all consumed alcohol to some extent. GGT activities ranged from 54 to 391 U/L. Two of these patients exhibited hepatomegaly on physical examination. Detectable serum ethanol concentrations were not found in any of these cases.

Three patients exhibited elevations in ALT less than that seen for AST, but had normal GGT activities. These patients were classified as having nonspecific liver changes.

Five cases of hepatitis B exposure or infection were discovered. Interestingly, none of these patients had reported a history of hepatitis or jaundice. All showed positive levels of hepatitis B core antibody while variable results were seen for the remaining serologies. The results of the serological profiles were consistent with recent acute infection (1 patient), chronic carrier status (2 patients), and past resolved infection (2 patients). None of these patients demonstrated persistence of the HBV_e antigen consistent with chronic hepatitis. AST activities in this group were only 42 to 80 U/L, and none exhibited hyperbilirubinemia.

Nine patients were classified as possessing elevated AST activities due to muscle insult or injury due to increased CK activities. One of these patients also exhibited an increase in LDH isoenzyme 5. CK isoenzyme determinations on these samples were all consistent with noncardiac, probably skeletal, muscle involvement due to the absence of significant CK-MB activity. None of these patients was thought to suffer from primary muscular disease; however, 2 patients were also biochemically hypothyroid and the enzyme changes were consistent with the muscle changes associated with this condition. Extensive physical exercise was the most probable cause for the enzyme changes in the remaining patients.

Of the 5 patients who could not be classified according to abnormalities in secondary tests directed by the computer algorithm, 3 probably represented insignificant elevations in AST activity (42–54 U/L). The data were incomplete for the 2 other patients.

Discussion

We have employed a computer-based EXPERT program in an effort to improve the information yield from outpatient AST determinations. Our application of EXPERT-directed sequential investigation to AST testing produced 74 positive interpretations in 3,096 patients. Confirmation of initial elevations revealed evidence for alterations in normal liver or muscle status that could have been overlooked if the initial profile results had been considered spurious in the absence of significant symptoms. Although determining an exact cause for these abnormal liver-function-test results was not always possible, we believe that this approach maximizes the available laboratory resources that may be applied to defining the etiology for the initial aminotransferase elevations. In this study, we found that only 5 of 79 abnormalities were not confirmed by abnormalities in additional labora-

tory tests. We believe that investigating a test abnormality to a point where maximum interpretative information may be made available to the physician is far more valuable in an outpatient setting than simple indicators of abnormality. This approach both minimizes the effect of apparently insignificant abnormalities and increases the confidence that significant pathology is present. These effects may lead to more informed medical decisions and lessen the probability of incorrect responses to the "unexpected" abnormality.

Assessment of the validity of laboratory-directed diagnostic conclusions in outpatients seen for routine health examination is difficult. Generally accepted clinical or histological criteria cannot be obtained and, as was seen in this study, definitive symptoms are rarely present. The only means available for estimating the accuracy of the conclusions is longitudinal follow-up. This portion of our study is still ongoing and will take several years to adequately evaluate. Preliminary results have shown, for example, that several patients classified here as having nonspecific liver dysfunction not due to hepatitis A or B may have alcohol-related liver changes because the enzyme results reverted to normal upon abstinence from alcohol. With more experience, the algorithm may be adjusted to improve accuracy and probabilistic quantitation may be applied to the conclusions. Nonetheless, the initial data substantiate the need for such investigations in outpatients as clear laboratory indicators of abnormality are certainly present.

To be successful as a high-volume routine procedure, this type of testing protocol requires the effective use of a computer. We used the EXPERT artificial intelligence program due to its inherent ease of programming and ability to incorporate the current knowledge concerning the relationships between test findings and clinical conditions. Additional advantages include the ability to maintain a data base of patient results that can be used to refine rules and interpretations based on our own experience. This approach can be applied to most tests on a routine laboratory screen. The incremental cost is less than the standard phlebotomy charge. We believe that significant unexpected pathology may be present in the outpatient setting and that sequential laboratory investigation represents a more effective alternative to traditional laboratory screening.

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