Assessment of the utility of aldolase determination in serum by monitoring patient outcomes*

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ABSTRACT

Serum aldolase (ALD) determination can be of some clinical interest in diseases of skeletal muscle. This study examined the pattern of ALD requesting in a general hospital and assessed the clinical utility of ALD activity measurement through examination of laboratory records, request forms, and case notes. Details of all serum ALD requests between December 1999 and October 2000 received by the laboratory at a 1200-bed hospital were extracted from the Laboratory Information System. The request forms from 100 random ALD requests were also inspected for clinical details. Clinical notes on 28 cases with increased ALD but normal creatine kinase (CK) activity results were inspected to see the effect of ALD measurement on patient outcome. Of the 600 ALD requests in 10 months, rheumatology/immunology was the most frequent requester (32%). Dermatomyositis/polymyositis, infections, and systemic lupus erhytematosus were the commonest indications on request forms. All ALD requests were accompanied with a simultaneous CK request. There was a moderate concordance between CK and ALD results (Kappa value, 0.46; 95% confidence interval: 0.38-0.53). In cases with increased ALD and normal CK activity, suspected muscle disease was the main reason for ALD measurement (86% of cases). There was no evidence that the increased ALD results led to any change in the further clinical evaluation, diagnosis, or treatment of any patient with non-elevated CK activity. Thus, ALD, in addition to CK measurement, appears to be of no clinical benefit. With the ready availability of CK measurement, it is questionable whether modern clinical laboratories should continue to offer ALD measurement at all.

RIASSUNTO

Valutazione della utilità della misura dell'aldolasi del siero basata sulla osservazione degli esiti dei pazienti

La determinazione della aldolasi (ALD) del siero può fornire indicazioni di un certo interesse nelle malattie del muscolo scheletrico. In questo studio è stato esaminato il profilo delle richieste di determinazione di ALD in un ospedale generale, ed è stata valutata l'utilità clinica della misura della attività dell'enzima mediante attento esame degli archivi di laboratorio, dei moduli di richiesta, e delle note cliniche relative ai singoli casi. I dettagli relativi a tutte le richieste di ALD ricevute dal laboratorio di un ospedale di 1200 letti, nel periodo Dicembre 1999-Ottobre 2000, sono stati estratti dal sistema informativo del laboratorio. Sono stati anche esaminati i dettagli clinici di 100 moduli di richiesta di ALD, scelti a caso. Sono state esaminate le annotazioni cliniche relative a 28 casi con aumentata ALD ma con normale attività della creatina chinasi (CK) per verificare l'effetto della misura della ALD sull'esito dei pazienti. La maggior parte (32%) delle 600 richieste di misura della ALD ricevute in 10 mesi derivava dalle unità di reumatologia/immunologia; le più frequenti indicazioni sui moduli di richiesta erano dermatomiositi/polimiositi, infezioni e Lupus Eritematoso Sistemico; tutte le richieste di ALD erano accompagnate da simultanea richiesta di CK. Si osservava una moderata concordanza tra i risultati di ALD e CK (valore kappa: 0,46%; intervallo di confidenza: 0,38 - 0.53). Nei casi con ALD aumentata e CK normale, il sospetto di malattia muscolare rappresentava la principale ragione per la misura della ALD (86% dei casi). Non vi era nessuna evidenza che valori aumentati di ALD condizionassero modificazioni della ulteriore valutazioni clinica, della diagnosi o del trattamento di alcun paziente con attività della CK non-aumentata. La misura della ALD in aggiunta a quella della CK non sembra quindi avere alcun vantaggio clinico. Disponendo della possibilità di misurare la CK, è pertanto discutibile se il laboratorio clinico moderno debba continuare a rendere disponibile a tutti la misura della ALD.

INTRODUCTION

Aldolase (EC 4.1.2.13; fructose-1,6-bisdiphosphate glyceraldehyde-3-phosphate-lyase; ALD) is an important enzyme in the glycolytic pathway, catalysing the conversion of fructose-1,6-diphosphate to dihydroxyacetone-

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phosphate and glyceraldehyde-3-phosphate. In muscle, ALD acts as a rapid response pathway for the production of ATP independent of oxygen. ALD is ubiquitous in the body but is most abundant in skeletal muscle, liver, and brain. Because of the diversity of tissues containing ALD, it is a very non-specific marker of tissue injury (1).

Despite its poor specificity, the measurement of ALD activity in serum is often requested to investigate muscle disease (2,3). The purpose of this audit was to examine the pattern of ALD requesting in a general hospital and assess the clinical utility of its measurement, particularly when it is requested together with serum creatine kinase (CK).

MATERIALS AND METHODS

The Department of Pathology and Laboratory Medicine at Tan Tock Seng Hospital services the inpatient and outpatient needs of a 1200-bed secondary level hospital with tertiary services in neuroscience and rheumatology/immunology. The laboratory offers onsite serum ALD and CK activity measurements. Determination of CK is available as an urgent test, 24 hours a day, on a Roche Hitachi 917 clinical chemistry analyser, using the IFCC recommended method at 37°C (4). The local reference interval for CK is 40-210 U/L for men and 38-164 U/L for women, repsectively. Determination of ALD activity is available as a batched test, run three times weekly on the same analyser, using a Roche Diagnostic assay kit at 37°C (5), with a local reference interval of 2.5-10 U/L.

Clinical and biochemical data (patient demographics, requesting discipline, and results of ALD and other simultaneously requested tests) on all serum ALD requests between December 1999 and October 2000 was downloaded from the Laboratory Information System (LIS) into a Microsoft Access database for further analysis. During September and October 2000, the order forms for 100 random ALD requests were inspected for clinical details. In particular, clinical notes on cases of discordant ALD and CK results (i.e., increased ALD with CK activity below the upper reference limit) were carefully examined to assess the possible effect of these results on patient management by clinicians.

Agreement between tests was quantified by the Kappa (K) statistic (6). Using this statistical approach, K is 1.00 when there is perfect agreement between the tests and <0.20 when the agreement is poor (7).

RESULTS

Data from LIS

Between December 1999 and October 2000, the laboratory received 600 requests for serum ALD activity determination. Details of requesting discipline and patient location are shown in Figure I. 66% of requests were on inpatients. Rheumatology-immunology was the single largest requesting discipline (24% outpatient, 8% inpatient). 52% of the ALD orders were for female (median age, 49 years) and 48% for male patients (median age, 47 years), respectively. All ALD requests were accompanied with a simultaneous CK request.

Concordance between CK and ALD results was shown in 73% of cases. 107 (18%) of patients showed only an increase of CK activity, whereas 53 (9%) of subjects showed an increase of ALD activity without any CK elevation. The Kappa statistics for agreement gave a K value of 0.36 (95% confidence interval (CI): 0.25-0.47) for male patients, 0.46 (95% CI: 0.35-0.57) for women, and 0.46 (95% CI: 0.38-0.53) considering all subjects, indicating fair to moderate agreement between the two assays.

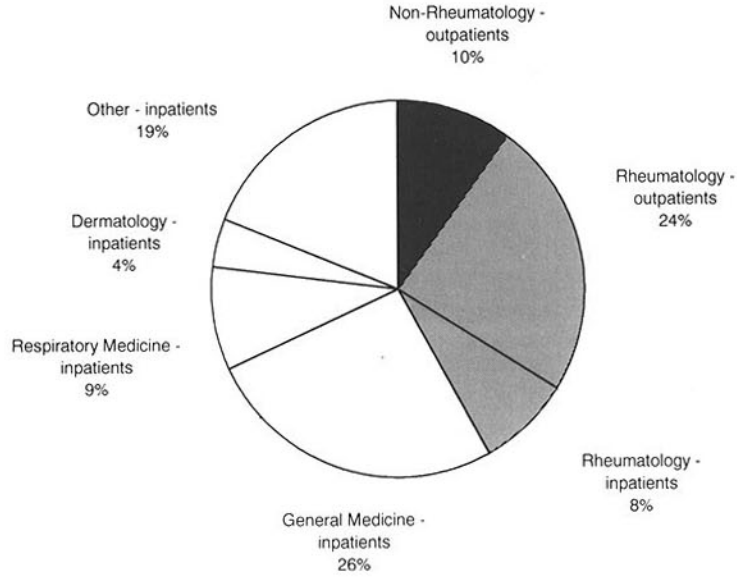

Figure I
Details of aldolase requesting discipline and patient location

Table 1
Summary of the examined cases with increased aldolase (ALD) activity in serum and creatine kinase below the upper reference limit

Report in case notes	ALD increase noted on report	ALD request written in notes	ALD result written in notes	Clinical diagnosis	Apparent indication for ALD request
Y	N	Y	Y	Dermatomyositis	Muscle inflammation
Y	N	N	Y	Dermatomyositis	Muscle inflammation
Y	Y	N	N	Dermatomyositis	Muscle inflammation
Y	Y	N	N	Dermatomyositis	Muscle inflammation
N	N	N	N	Dermatomyositis	Muscle inflammation
N	Y	Y	Y	Dermatomyositis	Muscle inflammation
N	N	N	N	Electrocution	Muscle disease
Y	Y	Y	N	Typhus	Myalgia
Y	Y	N	Y	Viral syndrome with myalgia	Myalgia
Y	Y	Y	Y	Disseminated tuberculosis with arthralgia	Muscle inflammation
Y	N	N	N	Thyrotoxicosis	Muscle inflammation
N	N	N	Y	Rhabdomyolysis	Rhabdomyolysis
N	N	N	N	Tension headache	Muscle inflammation
Y	N	Y	N	Myalgia	Muscle inflammation
N	N	Y	N	Pressure urticaria	Muscle inflammation
Y	N	Y	Y	Vasculitis	Muscle inflammation
Y	Y	Y	N	Drug overdose	Muscle inflammation
Y	Y	Y	N	Weakness	Muscle inflammation
Y	N	N	N	Musculoskeletal pain	Muscle inflammation
Y	N	Y	N	Weakness	Muscle inflammation
N	N	Y	N	Ocular myositis	Muscle disease
Y	N	N	N	Diabetes mellitus on pravastatin	Pravastatin monitoring
Y	Y	N	Y	Hypercholesterolemia on sinvastatin	Sinvastatin monitoring
Y	Y	Y	Y	Hypercholesterolemia on sinvastatin	Sinvastatin monitoring
N	N	N	N	Cellulitis	Routine in Rheumatology Division
Y	N	N	N	Cerebrovascular accident	Weakness
Y	N	N	N	Malaria	Aminotransferase increase
N	N	N	N	Tuberculosis reactivation	Weakness

Data from request forms

The clinical details from the 100 request forms randomly selected were carefully inspected. 57% of requests had no clinical details. Of those with clinical details, infections (e.g., pneumonia, sepsis) and dermatomyositis/polymyositis were the commonest indications given, followed by systemic lupus erhytematosus. A previous increased CK acitivity was mentioned in 2% of requests (Figure II).

Data from case note inspection

30 of the 53 cases in which ALD activity alone was elevated were chosen at random for inspection of clinical notes. 28 out of 30 case notes could be traced.

The results are shown in Table 1. Laboratory reports were found in clinical notes in 68% of cases. The ALD increase was noted on the report in 53% of cases. Initiation of the request was written in the notes in 12/28 (43%) cases and the increased ALD result was commented on or written in the notes in 9/28 (32%). The commonest final clinical diagnoses were dermatomyositis and infections with suspected myalgia (21% each). Evaluation for the presence of a muscle disease was the main indication for ALD measurement (21/28, 75%), with monitoring of asymptomatic hypercholesterolemic patients treated with hydroxy-methylglutaryl coenzyme A (HMG-CoA) reducta-se inhibitors comprising another 11% of cases. In no case,

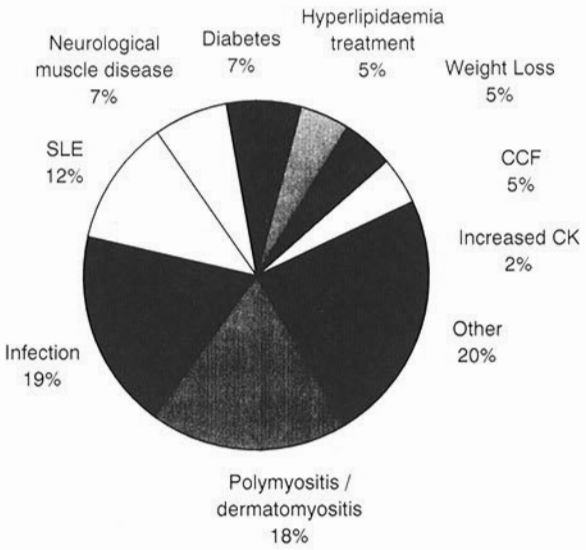

Figure II
Clinical details from aldolase request forms.
SLE, systemic lupus erhytematosus; CCF, congestive cardiac failure; CK, creatine kinase

the discrepancy between CK and ALD results was commented upon. Above all, there was no evidence from inspection of the clinical notes that the ALD elevation led to any change in the further evaluation, diagnosis, or treatment of any patient.

DISCUSSION

The picture derived from this audit is that, in our clinical setting, ALD is always requested together with CK and is used in the evaluation of musculoskeletal disease or symptoms, with rheumatology/ immunology being the single largest requester. This pattern is similar to that previously described, with musculoskeletal disease predominating as a clinical indication for ALD requesting (8). However, this use of ALD in the initial evaluation (inpatients and outpatients) and monitoring (outpatients) of musculoskeletal disease has little published evidence. ALD is not as specific for muscle as CK and does not correlate as well with disease activity as do CK and aspartate aminotransferase (AST) (2,3,9). Given that the ALD concentration in red cells is ten times that of plasma, even small degrees of sample haemolysis can increase ALD activities, limiting the test's clinical utility further (10). Because of its greater sensitivity and ease of measurement, CK is generally considered the enzyme of choice in investigation of skeletal muscle disease (3,11). A recent review on evaluation of rhabdomyolysis made no mention of ALD measurement (12). It has been suggested that ALD can be useful for distinguishing myopathy from muscle atrophy when used in conjunction with the CK/AST ratio, but there was no evidence of its use in this fashion from this audit (2).

The moderate agreement between CK and ALD activity concentrations seen in both this audit and previously (8) might suggest that ALD measurement in addition to CK could give additional information to the clinician and result in a change in patient management. The clinical notes of the subgroup of raised ALD with non-elevated CK cases were examined further for evidence of this. The lack of evidence that increased ALD, even when noted and written in the medical records, led to any change in patient management militates however against any significant additional practical value in ALD measurement.

In conclusion, this audit demonstrated that in our hospital ALD is always requested together with CK in the evaluation and monitoring of musculoskeletal disease. Despite lack of concordance between CK and ALD results, there is no evidence that ALD measurement, in addition to CK, was of clinical value in the patients studied. The present practice of routine simultaneous ALD and CK requesting should thus be discouraged. With the ready availability of CK measurement, it is questionable whether modern clinical laboratories should continue to offer ALD measurement at all.

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