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Serum enzyme studies in muscle disease

Part II Serum creatine kinase activity in muscular dystrophy and in other myopathic and neuropathic disorders

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It has been established that the levels of certain enzymes are elevated in the serum of patients suffering from muscular dystrophy. Previous studies (Pearson, 1957; Dreyfus, Schapira, and Demos, 1958; Thompson and Vignos, 1959; Schapira, Dreyfus, Schapira, and Demos, 1960; Thomson, Leyburn, and Walton, 1960; Pearson, Chowdhury, Fowler, Jones, and Griffith, 1961) have indicated that a number of different serum enzymes, including aldolase, transaminases, lactate dehydrogenase, and phosphohexoseisomerase, may be found to have abnormally high activity in such cases.

Comparative studies in affected patients have shown that the serum creatine kinase is more satisfactory than the other enzymes mentioned above for diagnostic purposes in cases of clinical and preclinical muscular dystrophy, and is also useful in discriminating other forms of dystrophy from the Duchenne type (Chung, Morton, and Peters, 1960; Aebi, Richterich, Colombo, and Rossi, 1962; Dreyfus and Schapira, 1962; Hughes, 1962; Richterich, Rosin, Aebi, and Rossi, 1964).

Most recent reports have been confined to relatively small numbers of patients, and deal mainly with the Duchenne variety of muscular dystrophy. Physiological variations in serum creatine kinase activity have recently been described in normal subjects (Pearce, Pennington, and Walton, 1964). Against this background, the present paper gives our findings in a series of patients suffering from the more common varieties of muscular dystrophy and in patients with non-hereditary myopathic disorders, as well as in a number of patients with muscular weakness and wasting of neuropathic origin, in order to delineate more precisely the diagnostic value of serum creatine kinase estimations in these conditions.

MATERIALS AND METHODS

The patients were classified according to the criteria of Walton and Nattrass (1954), as subsequently modified by Walton (1961), into Duchenne, limb-girdle, and facioscapulohumeral types, and a number of cases of dystrophia myotonica were included. The non-hereditary myopathies have been subdivided into cases of polymyositis and a miscellaneous group. This latter group includes cases of myopathy associated with connective tissue disorders, metabolic diseases, and cases induced by corticosteroid drugs. The diagnosis was based on clinical data, and in any case where this was in doubt, electromyography and muscle biopsy were used to confirm the clinical diagnosis.

Physical exercise, the ingestion of food, and certain other physiological variables do not affect the serum creatine kinase level (Pearce *et al.*, 1964) and therefore no account was taken of these factors in obtaining blood samples.

The creatine kinase activity of serum was estimated by measuring the formation of creatine from creatine phosphate and adenosine diphosphate; the details of the method have been described in a previous paper (Pearce *et al.*, 1964). The results are expressed as micro-moles of creatine formed per hour per millilitre of serum at 37°C.; the upper limit of normal is 3·5 units in this laboratory.

RESULTS

The results are given in Tables I to VII. In all 21 patients with Duchenne dystrophy the serum creatine kinase level was grossly elevated, values ranging from 70 to 962 units; the elevation was maximum in the younger cases of shortest duration (Fig. 1). Four out of six cases of limb-girdle dystrophy exhibited abnormally high levels, namely, between 5 and 99 units. Of seven cases of facioscapulohumeral dystrophy, all had abnormal creatine kinase activity, varying between 3·8 and 17 units. Five out of seven cases of dystrophia myotonica had elevated creatine kinase activity, values varying from 3·9 to 9 units.

In the non-hereditary myopathies, only four out of 12 cases of polymyositis showed abnormal values, and all 17 patients with myopathy associated with connective tissue diseases, metabolic diseases, and steroid therapy had normal serum creatine kinase activity.

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TABLE I

SERUM CREATINE KINASE ACTIVITY IN THE DUCHENNE TYPE OF MUSCULAR DYSTROPHY

Patient	*Age of Onset (yr.)*	*Present Age (yr.)*	*Duration of Disease (yr.)*	*Creatine Kinase Activity (units)*
K.B.	1½	4	2½	452
D.L.	2	5	3	962
J.O.	2	5	3	540
D.S.	2	6	4	696
B.P.	3	6	3	397
C.T.	1½	6	4½	383
P.J.	2	7	5	440
A.L.	1	7	6	582
A.P.	2½	7	4½	481
J.L.	3	7	4	230
C.C.	3	8	5	136
J.C.	1½	8	6½	833
A.S.	3	8	5	250
K.C.	2½	9	6½	159
A.L.	2	9	7	140
G.A.	4	10	6	366
M.C.	4	10	6	178
T.N.	2½	11	8½	256
D.W.	4	13	9	178
M.P.	9	15	6	70
J.W.	Not known	43	c. 35	113

TABLE II

SERUM CREATINE KINASE ACTIVITY IN LIMB-GIRDLE DYSTROPHY

Patient	*Age of Onset (yr.)*	*Present Age (yr.)*	*Creatine Kinase Activity (units)*
M.L.	15	19	99.0
K.W.	20	25	40.0
J.P.	23	39	1·6
W.E.	16	49	8·8
T.C.	12	42	5·1
L.C.	14	17	1·8

TABLE III

SERUM CREATINE KINASE ACTIVITY IN FACIOSCAPULO-HUMERAL DYSTROPHY

Patient	*Age of Onset (yr.)*	*Present Age (yr.)*	*Creatine Kinase Activity (units)*
M.B	20	20	10·6 9·3
L.C.	20	52	15·0
A.C.	33	47	6·7
J.J.	35	41	5·8
M.O.	23	27	3·8
O.A.	24	30	9·2
E.R.	20	22	17·8

TABLE IV

SERUM CREATINE KINASE ACTIVITY IN DYSTROPHIA MYOTONICA

Patient	*Age of Onset (yr.)*	*Present Age (yr.)*	*Creatine Kinase Activity (units)*
R.C.	18	19	3·9
M.G.	38	40	2·9
J.S.	22	27	9·0
J.S.	23	25	3·5
J.A.	36	41	6·5
R.B.	31	43	6·7
A.T.	–	3	3·7

TABLE V

SERUM CREATINE KINASE ACTIVITY IN POLYMYOSITIS

Patient	*Age (yr.)*	*Diagnosis*	*Creatine Kinase Activity (units)*
J.C.	48	Chronic polymyositis	2·6
W.M.	40	Chronic polymyositis treated with steroids	77·4
M.U.	45	Chronic polymyositis	0·9 1·6
E.H.	54	Chronic polymyositis	1·2
T.D.	61	Acute polymyositis	11·4
J.P.	18	Subacute polymyositis	1·8
E.D.	64	Chronic polymyositis	3·4
P.D.	3½	Subacute polymyositis	8·1 4·9
G.O.	32	Chronic polymyositis	0·9
D.A.	40	Chronic polymyositis	1·6
J.E.	8	Chronic polymyositis	119
S.H	50	Chronic polymyositis	1·3

TABLE VI

SERUM CREATINE KINASE ACTIVITY IN OTHER MYOPATHIES

Patient	*Age (yr.)*	*Diagnosis*	*Creatine Kinase Activity (units)*
L.B.	41	Rheumatoid disease with myopathy	0·8
J.B.	73	Carcinomatous myopathy	2·9
A.D.	46	Carcinomatous myopathy	0·7
M.W.	53	Thyrotoxic myopathy	1·6
H.L.	35	Thyrotoxic myopathy	1·6
H.C.	53	Rheumatoid disease steroid-treated	0·9
A.A.	48	Polymyalgia rheumatica	2·3
D.C.	51	Systemic sclerosis	1·8
M.W.	71	Dermatomyositis	3·5
L.T.	43	Rheumatoid disease steroid-treated	0·7
J.R.	75	Polymyalgia rheumatica	0·9
A.K.	57	Steroid myopathy (B)[1]	2·9
B.T.	61	Steroid myopathy (D)[2]	2·0
E.G.	67	Steroid myopathy (B)	0·7
F.B.	49	Steroid myopathy (B)	2·4
H.F.	46	Steroid myopathy (D)	0·9
S.C.	56	Steroid myopathy (B)	1·7

[1]Betamethasone
[2]Dexamethasone

TABLE VII

SERUM CREATINE KINASE ACTIVITY IN NEUROGENIC MUSCLE DISEASE

Patient	*Diagnosis*	*Creatine Kinase Activity (units)*
R.R.	Cervical spondylosis	1·6
O.H.	Polyradiculopathy with muscular wasting	1·3
J.H.	Disseminated sclerosis	1·5
H.M.	Syringomyelia	1·6
V.C.	Lumbar spondylosis	1·7
R.A.	Neuralgic amyotrophy	1·8
M.A.	Cauda equina compression (lumbar disc lesion)	1·0
C.C.	Déjèrine-Sottas syndrome	1·5
A.McC.	T.1 root compression with muscular atrophy	1·4
A.C.	Motor neurone disease	3·0
R.K.	Motor neurone disease	1·5
F.K.	Motor neurone disease	1·0
E.A.	Werdnig-Hoffman disease	1·7

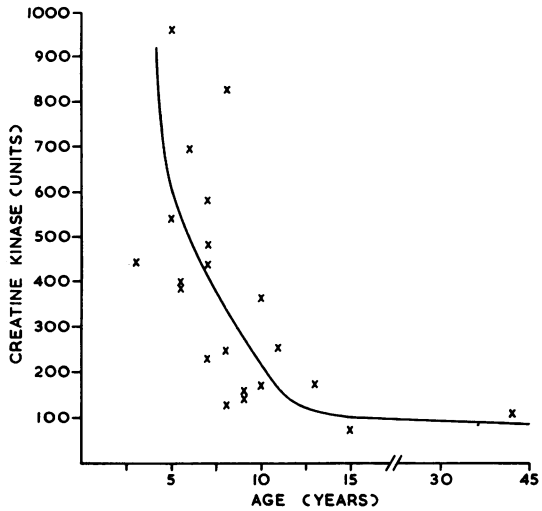

FIG. 1. *Activity of the serum kinase in cases of the Duchenne type of muscular dystrophy charted against the patients' ages.*

In a series of cases of neurogenic muscle disease, the serum creatine kinase activity was normal.

DISCUSSION

From the results obtained, it is suggested that estimation of the serum creatine kinase activity is of considerable diagnostic value. The activity of this enzyme is constantly and grossly elevated in cases of Duchenne type muscular dystrophy, this elevation being maximum in the younger patients with disease of shortest duration (Fig. 1). This is in agreement with the findings for serum aldolase in other studies (Pearson, 1957; Thompson and Vignos, 1959; Thomson *et al.*, 1960).

In the other inherited myopathies, the serum creatine kinase level was elevated in the majority of cases, but the elevation observed was considerably less than that found in patients with the Duchenne type of dystrophy. As Richterich and his co-workers point out (1964), the serum creatine kinase level is thus of value in the occasional case, where clinical diagnosis is difficult, in discriminating between the Duchenne type and the other hereditary types of muscular dystrophy. It is of interest that the only case of muscular dystrophy which was believed not to be the Duchenne type, and in which serum creatine kinase activity approached the level seen in the Duchenne group (M.L., Table II), exhibited gross pseudohypertrophy of the calf muscles. This feature, which is seen in a proportion of cases of limb-girdle dystrophy (Walton and Nattrass, 1954), cannot be related causally to the high enzyme level, but undoubtedly pseudohypertrophy and very high enzyme levels frequently coexist in patients with the Duchenne type of dystrophy. In this case the clinical diagnosis of limb-girdle dystrophy was made independently by two of us (J.N.W. and J.M.S.P.), but it is conceivable that this case could be an example of that type of Duchenne dystrophy which is of relatively late onset and runs a more benign course. Conversely, it is possible that another case (M.P., Table I), classified by both of us as a Duchenne type case of comparatively late onset, but in which the serum creatine kinase activity was only 70 units, could be included in the limb-girdle group on the basis of the clinical and the enzyme findings. However, a younger brother exhibits classical signs of Duchenne type dystrophy and has a serum creatine kinase level of 397 units. Nevertheless, the serum creatine kinase could conceivably prove to be a more sensitive indicator of the Duchenne type of dystrophy than clinical examination.

In the past, elevated activities of serum transaminase and of aldolase have been observed in patients suffering from polymyositis. In the present study most cases of polymyositis had normal serum creatine kinase levels. Two children (P.D. and J.E., Table V) showed markedly elevated values, and in one man (W.M., Table V), who was being treated with prednisone, there was also a marked increase in the serum creatine kinase. It was this observation which prompted a study of enzyme activity in cases of steroid myopathies, in which group, however, we were unable to demonstrate any abnormality in serum creatine kinase. In cases of polymyositis, we were unable to find any clear-cut correlation between the chronicity or activity of the disease, and the elevation occasionally observed in serum creatine kinase. In some cases showing a normal activity of this enzyme in the serum, there was widespread muscular weakness and the disorder was comparatively acute. Both children with polymyositis exhibited high serum creatine kinase levels, and it may be that in this condition the level is more related to age than to the activity of the disease. The elevation is so infrequent in adults as to be of no diagnostic value, though a normal figure favours polymyositis as opposed to muscular dystrophy of late onset.

It has been shown by Schapira and his co-workers (1960) that although the serum aldolase and transaminases were found to be elevated in the primary myopathic disorders, these enzymes were present in normal amounts in the sera of patients with neurogenic muscular atrophy. Our results demonstrate that the serum creatine kinase activity is also normal in patients with neurogenic muscle disease, and hence is of considerable value in differentiating

such patients from cases of muscular dystrophy. This accords with the findings of Pearson (1962).

The serum transaminases are frequently elevated to equally high levels both in cases of polymyositis and in cases of muscular dystrophy. Serum aldolase is similarly often elevated in both conditions, but the levels are usually lower in polymyositis. However, differentiation between these two groups of muscle disease cannot be made with confidence on the basis of changes of the serum levels of these enzymes. The almost constant elevation of serum creatine kinase levels in cases of muscular dystrophy, compared with the occasional and comparatively small elevation which occurs in patients suffering from polymyositis, is of considerable diagnostic value in differentiating these two conditions in cases where the clinical diagnosis is in doubt. However, our findings suggest that serum creatine kinase activity is perhaps of less value in this connexion when distinguishing childhood polymyositis from dystrophy.

It is well known that intracellular enzymes may be liberated into the serum as a result of local inflammation or ischaemic necrosis. Elevations of serum creatine kinase activity may therefore be found in patients suffering from myocardial or hepatocellular disease. Recent reports (Graig and Ross, 1963; Griffiths, 1963; Saito, Hibi, Kawazura, and Fukuyama, 1963) have indicated that similar elevations are found in cases of hypothyroidism, and that the elevation may be reversed by appropriate replacement therapy (Saito *et al.*, 1963). The presence of the above diseases will usually be apparent from the clinical features of the individual case, and in our experience have not been a source of diagnostic difficulty in patients with primary muscular disorders.

It is important to note that the results obtained in this study must be related to the biochemical method used in estimating serum creatine kinase. Differing results have been obtained in patients with polymyositis by Richterich and his co-workers (1964), who employed a different and more complex technique for serum assays of creatine kinase, and these results have yet to be confirmed.

The finding of increased levels of muscle enzymes in the serum is thought to represent an abnormal permeability of the muscle cell membrane which allows the enzymes to leak out into the plasma (Thomson *et al.*, 1960; Thomson, 1962). The highest values occur in the early stages of muscular dystrophy, and the levels decline in parallel with the diminution of functional muscle mass (Thompson and Vignos, 1959). Almost certainly the leakage of muscle enzymes into the serum represents a secondary effect of muscle cell dysfunction, and is not of primary aetiological significance. The difference between the serum creatine kinase levels we have found in the muscular dystrophies and those recorded in the acquired myopathies is striking, and as an empirical observation is of some help in diagnosis. The significance of this finding is not immediately apparent but could reflect certain basic differences in the pathogenesis of the two groups of diseases. It seems possible that the dystrophic process, in addition to producing degeneration and necrosis of muscle cell cytoplasm and nuclei, selectively damages the muscle cell membrane; this process appears to be most marked in the most rapidly destructive variety of muscular dystrophy, namely the childhood or Duchenne type.

SUMMARY

The serum creatine kinase activity has been measured in a series of patients suffering from the common types of muscular dystrophy, and in cases of acquired myopathy. Constant elevation of serum creatine kinase activity was found in the Duchenne type cases, and smaller elevations were noted in limb-girdle and facioscapulohumeral cases and in dystrophia myotonica. In the acquired myopathies, including polymyositis, the enzyme level was usually normal except in cases of polymyositis in childhood. The diagnostic significance of these findings and certain aetiological implications are discussed.

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