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Creatine Phosphokinase Activity in Newly Admitted Psychiatric Patients

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Introduction

Increased serum creatine phosphokinase (C.P.K.) levels have been shown in acutely psychotic patients on admission to hospital (Meltzer, 1968). Little is known about C.P.K. activity in non-psychotic (e.g. neurotic) patients admitted under similar conditions. Psychotic patients have not been compared with non-psychotic patients over a period of time following admission. Examination of a single serum sample for C.P.K. activity in non-psychotic patients at the time of admission has shown no abnormality (Meltzer *et al.*, 1969).

C.P.K. is an intracellular enzyme and increased activity in serum has been shown to occur in the following conditions: myocardial infarction (Sorensen, 1963), cerebral vascular disease (Acheson *et al.*, 1965), muscular dystrophy (Hughes, 1962) and myxoedema (Craig and Smith, 1965). The enzyme C.P.K. exists in three molecular forms. Type I is found almost exclusively in the brain, Type II in cardiac muscle and Type III in skeletal muscle (Burger *et al.*, 1964) and it is possible to separate the enzyme into its isoenzymes by electrophoretic separation and subsequent histochemical staining. Type III is the isoenzyme found in the serum of psychotic patients. It is not clear why the skeletal muscle isoenzyme should be raised in psychotic states. However, certain subclinical muscle myopathies have been implicated as the site of enzyme release (Meltzer and Moline, 1970). Drugs taken by mouth do not cause an increase in serum C.P.K. (Meltzer *et al.*, 1969) but it has been shown that intramuscular chlorpromazine causes an increase in C.P.K. activity in a proportion of patients (Meltzer *et al.*, 1969). Physical activity, severe emotional stress not part of a psychotic process, weight loss, hypersecretion of steroids or epinephrine and muscle tension may cause increased enzyme activity in some patients. They do not cause the high C.P.K. activity seen in acutely psychotic patients (Meltzer and Moline, 1970).

The C.P.K. changes in acute psychotic patients are usually transient and episodic. These elevations are easily missed due to the time lapse between onset of the psychosis and admission to hospital. The reported median number of days with raised serum C.P.K. in acutely psychotic patients is ten days (Meltzer *et al.*, 1969). The enzyme C.P.K. persists in the serum after acute episodic release, e.g. myocardial infarction, for about two days. Raised levels in psychotic patients can last for ten or more days and suggest a process of continued enzyme release.

A problem that arises when studying any hospital population is that findings may be due to factors associated with the routine of the ward, but this can be avoided by comparing groups of psychotic and non-psychotic patients admitted to the same ward and nursed under the same conditions. Surprisingly little is known about the rating behaviour and diagnostic habits of psychiatrists (Copeland *et al.*, 1971) and this causes difficulty in comparing groups of patients. The In-Patient Multidimensional Psychiatric Scale (Lorr and Klett, 1967) is a satisfactory and practical compromise allowing valid and reliable comparisons to be made in clinical studies (Kerry and Orme, 1972).

The present study examines:

(a) the proportion of psychotic and non-psychotic patients showing raised serum C.P.K. activity;

(b) the relationship between the I.M.P.S. profiles of psychotic activity and C.P.K. activity;

and (c) the value of serum C.P.K. estimations in screening for the presence of psychotic illness.

Methods

Selection of patients

The treatment received by each patient before admission was reviewed and any patient with a history of an intramuscular injection or

of an overdose of drugs likely to cause raised serum C.P.K. activity (Wright *et al.*, 1971) were excluded from the study. Only patients having orally administered drugs were included and any patient having an intramuscular injection after admission was excluded. Some patients were not included because they objected to blood samples being taken. Then the first 18 acutely psychotic female patients admitted were studied. All psychotic diagnoses were accepted. Selection occurred fortuitously to some extent since most admissions were determined by the firm being on take at the time.

Two longer stay patients on the same ward were also included. The first patient was a 64-year-old woman. She had recurrent depressive illnesses; two attacks of manic behaviour had followed treatment for depression. She had been first admitted to hospital in 1954, since when she had been admitted fifteen times. As is common with the affective disorders, her attacks had become progressively more frequent, and she had spent most of the past ten years, and all of the past three years, in hospital. Each illness lasted from two to three weeks, separated by intervals of three to four weeks when she was free from symptoms.

The second patient was a woman 39 years old. She had her first attack of depression in a manic-depressive illness about five years ago. Her last admission had been two years before, and, apart from three short periods at home, she had been in hospital ever since. Her illness took a regular and recurrent form in which a three-week period of depression was followed by two weeks of hypomania. She had about seven days of stable mood between attacks.

A control group was the first 12 clearly non-psychotic female patients admitted during the same time (Table I, patients 21–32). Both groups were on the ward concurrently and subject to the same environmental influences. The clinical diagnosis and the I.M.P.S. rating were done before any treatment was given which might affect the psychiatric examination.

In-Patient Multidimensional Psychiatric Scale

The I.M.P.S. measures, in an interview, psychotic syndromes established by repeated factor analysis (Lorr and Klett, 1967). Five second-order factors have been identified and have been called disorganized hyperactivity, schizophrenic disorganization, paranoid process, anxious depression and hostile paranoia. These factors cover the dominant characteristics of the major groupings of psychosis: mania, depression, non-paranoid schizophrenia and paranoid schizophrenia. It is a reliable and valid technique (Lorr and Klett, 1968, 1969a, 1969b), the results of which are related to the diagnosis and degree of illness. The I.M.P.S. was given as recommended, with two raters (R.J.K. and J.E.O.).

Creatine phosphokinase measurements

Blood was taken as soon as possible after admission and subsequent samples were taken daily at about 8 a.m. The procedure was the same for both psychotic and neurotic patients. The C.P.K. activity at 35 °C. was measured by linking the C.P.K. catalysed reaction through hexokinase to one involving glucose-6-phosphate dehydrogenase and the conversion of nicotinamide adenine dinucleotide phosphate to its reduced form. Glutathione was included within the reaction mixture to 'activate' the C.P.K. The increase in optical density at 340 nanometres due to the formation of reduced nicotinamide adenine dinucleotide phosphate was plotted using an L.K.B. 8600 reaction rate analyser and was directly proportional to the C.P.K. activity. The reagents used were supplied by Boehringer Corporation in the form of a test kit for C.P.K. determination (Cat. No. 15926. TCAF). Solutions were prepared as recommended and the reaction started by the automatic addition of 75 μl. of creatine phosphate (Solution 3) by the dispenser of the L.K.B. 8600 analyser to the assay system. Only half the recommended test quantities were used as the L.K.B. 8600 requires a minimum value of only 1 ml. in each test cuvette.

By measuring the gradient of the graph (optical density against time), the C.P.K. activity in milli units/millilitre (mU./ml.) was calculated. Normal values were established on 72 healthy volunteers and found to be 10–60 mU./ml. for females and 10–105 mU./ml. for males. Only women were subjects of the present study.

Results

The findings are shown in Table I. For each patient this gives the clinical diagnosis, the maximum serum C.P.K. activity and the scores obtained on the five second-order syndromes of the I.M.P.S. The results show that raised serum C.P.K. is seen only in patients with psychotic illnesses and is not present in any of the non-psychotic patients. It can be seen that with one exception (patient number 11) there is a clear distinction in C.P.K. values between the psychotic patients with raised serum C.P.K. and those with normal serum C.P.K. values.

Table II shows the relationship between clinical diagnosis and the presence of normal or raised serum C.P.K. activity. Tables III and IV show the relationship between the five second-order factors of the I.M.P.S. and serum C.P.K. activity. It is seen that raised serum C.P.K. activity is more common in mania and paranoid schizophrenia than in depression and non-paranoid schizophrenia. Although this is only a trend when the clinical diagnosis is used, with the I.M.P.S. factors it is statistically significant ($P < 0{\cdot}01$). Table I also shows that 50 per cent of the psychotic patients (10 out of 20) have raised serum C.P.K. activity. Only one neurotic patient was originally found to have a raised serum C.P.K. (210 mU./ml.) and was later excluded because she had myxoedema

TABLE I

Clinical diagnosis, C.P.K. values and I.M.P.S. second order factor scores in female patients

	Age	Clinical diagnosis	Peak serum C.P.K. activity mU./ml.	I.M.P.S. second order factor scores				
				Dis-organized hyper-activity	Paranoid process	Hostile paranoia	Schizo-phrenic disorga-nization	Anxious depression
1.	44	Mania	145	67*	38	38	38	40
2.	48	Mania	810	63*	40	38	38	50
3.	54	Mania	430	65*	40	41	40	43
4.	41	Mania	937	63*	35	53	40	41
5.	59	Mania	350	74*	34	50	39	46
6.	24	Schizophrenia	230	47	76*	47	43	49
7.	64	Endogenous depression ..	639	58*	42	39	48	77*
8.	44	Paranoid schizophrenia ..	366	39	78*	41	51	41
9.	30	Paranoid schizophrenia ..	111	39	33	71*	54	39
10.	42	Paranoid schizophrenia ..	550	48	56*	50	45	50
11.	47	Mania	92	75*	38	38	38	45
12.	46	Mania	40	56	51	38	41	50
13.	65	Endogenous depression ..	43	46	48	38	42	66*
14.	57	Endogenous depression ..	64	40	50	38	48	66*
15.	64	Endogenous depression ..	43	47	46	38	52	73*
16.	62	Endogenous depression ..	38	42	50	38	43	57*
17.	55	Endogenous depression ..	45	50	46	43	45	80*
18.	45	Endogenous depression ..	55	38	48	41	56*	71*
19.	23	Schizophrenia	38	43	50	39	75*	34
20.	36	Paranoid schizophrenia ..	36	42	44	52	43	45
21.	36	Anxiety state	36	45	49	38	40	56
22.	43	Anxiety state	53	47	48	38	39	53
23.	37	Anxiety state	28	46	48	38	45	45
24.	51	Neurotic depression ..	47	41	54	43	47	70*
25.	34	Neurotic depression ..	66	46	44	48	40	63*
26	40	Neurotic depression ..	49	48	41	53	41	52
27.	39	Neurotic depression ..	45	46	45	46	39	58*
28.	75	Neurotic depression ..	70	47	48	38	40	63*
29.	24	Neurotic depression ..	53	42	50	38	42	68*
30.	50	Neurotic depression ..	32	49	44	43	39	51
31.	38	Neurotic depression ..	66	45	48	39	39	64*
32.	25	Neurotic depression ..	43	59*	39	46	40	68*

* Score at or above the 80th percentile.

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(protein-bound iodine 1·8 μg./100 ml. and serum cholesterol 392 mg./100 ml.).

TABLE II
Diagnosis and C.P.K.

	(a) Mania	(b) Paranoid schizophrenia	(c) Endogenous depression	(d) Schizophrenia	(e) Neurotics
Raised C.P.K. ..	5	3	1	1	0
Normal C.P.K...	2	1	6	1	12

(chi squared of a − b v. c + d = 3·24 (d.f.l., Yates) P < 0·10)

TABLE III
C.P.K. and factor scores on disorganized hyperactitity, paranoid process and hostile paranoia for the 20 psychotics

	At least one score at 80 percentile or over	All less than 80 percentile
Raised C.P.K. ..	10	0
Normal C.P.K...	1	9

chi² = 12·84 (d.f.l. Yates) P < 0·01. Only 1 or 12 neurotics had a score at or above the 80 percentile for any of the 3 factors. With the psychotic group this would give a chi² = 20·51 (d.f.l. Yates) P < 0·01

TABLE IV
C.P.K. and factors scores on schizophrenic disorganization and anxious depression for the 20 psychotics

	One score at 80 percentile or over	Both less than 80 percentile
Raised C.P.K. ..	1	9
Normal C.P.K...	7	3

(chi² = 5·21 (d.f.l. Yates) P < 0·05. Seven of the 12 neurotics had a score at the 80 percentile or above on the anxious depression scale. Added to the psychotic group, this would raise the chi² to 5·93 (d.f.l. Yates) P < 0·05)

DISCUSSION

Ten out of 20 psychotic patients studied here had a large increase in serum C.P.K. This increase was associated with the psychotic illness itself rather than environmental or any other factors associated with admission to hospital. A control group of non-psychotic (neurotic) patients admitted at the same time and studied for C.P.K. activity for at least a week each did not show any increase in serum C.P.K. It could be argued that the increased serum C.P.K. activity might have been the cause of the psychotic illness but this is unlikely as even greater increases are found in some patients with primary muscle disorders (e.g. Duchenne muscular dystrophy) who have little or no mental disturbance. The problem arises why this increase was seen in only half the psychotic patients studied?

One possibility is that the enzyme changes are transient, often lasting for only a few days, and usually occurring at the beginning of the illness which is usually the period of the greatest psychotic turmoil. Most patients are only admitted to hospital after they have been ill for at least some days by which time the serum C.P.K. may have been increased and have already returned to normal. Two of the patients in this series (numbers 3 and 5) had also been attending the out-patient department for more than a year. Both had had high C.P.K. activity prior to acute psychotic illnesses which caused their admission to hospital. For example, patient number 3 was seen at the out-patient department with a serum C.P.K. of 132 mU./ml. although she was clinically well at that time. She was admitted to hospital in mania 5 days later when her C.P.K. was 222 mU./ml. This shows that the changes may occur early in the illness and be easily missed. The presence of a raised serum C.P.K. in an out-patient (without there being a physical cause) maybe a warning that a psychotic breakdown is imminent.

Another possibility is that there may be different groups of psychotic illnesses varying in C.P.K. activity. Previous studies have not included any complete attempt to relate changes in enzyme activity with the profiles from a psychotic rating scale such as the I.M.P.S. The findings here show that patients with mania and paranoid schizophrenia tend to have the largest increase in C.P.K. activity. It is interesting that the only patient in Table III with a normal serum C.P.K. and at least one score over the 80th percentile on the I.M.P.S. hyperactivity and paranoid factors was patient number 2, where the C.P.K. activity was 92 mU./ml. (i.e. above the normal range for women but below that for men). She was considered not to be raised in C.P.K. activity as this figure might be a doubtful increase for statistical purposes.

Three patients in this series with raised C.P.K. activity have now been seen with subsequent attacks of psychotic illness. On these occasions, each individual has had the same clinical diagnosis and I.M.P.S. profile as previously.

Our conclusions are that about 50 per cent of our newly-admitted psychotic patients have raised C.P.K. activity, and this is related to particular psychotic profiles on the I.M.P.S. Raised serum C.P.K. suggests that psychotic illness may be present and that the illness is more likely to be mania or paranoid schizophrenia than either depression or non-paranoid schizophrenia. C.P.K. measurements are useful in psychiatric practic and if these are abnormally high the patient should have further psychiatric or physical investigation. This view is strengthened because we found clinically stable outpatients with increased C.P.K. activity who were admitted to hospital a few days later for psychotic illnesses. The only non-psychotic we have seen with raised C.P.K. activity had myxoedema. We feel that C.P.K. estimations are useful both on the ward and in the outpatient clinic.

Summary

Raised serum C.P.K. activity has been shown to occur in physical disorders and in acute psychosis. In the latter (and in certain physical disorders) it is the skeletal muscle isoenzyme which is raised. This study shows that about half of newly-admitted psychotic patients have raised C.P.K. activity. This is related to the I.M.P.S. psychotic profiles of mania and paranoid schizophrenia rather than to those of depression and non-paranoid schizophrenia. Raised C.P.K. activity indicates the presence of psychotic or physical illness.

References

Acheson, J., James, D. C., Hutchinson, E. C., and Westland, R. (1965). 'Serum creatine kinase levels in cerebral vascular disease.' *Lancet*, *i*, 1306–7.

Burger, A., Richterich, R., and Aebi, H. (1964). 'Die Heterogenität der Kreatin-Kinase.' *Biochemische Zeitschrift*, 339, 305–14.

Copeland, J. R. M., Cooper, J. E., Kendell, R. E., and Gourlay, A. J. (1971). 'Differences in usage of diagnostic labels amongst psychiatrists in the British Isles.' *British Journal of Psychiatry*, 118, 629–40.

Craig, F. A., and Smith, J. C. (1965). 'Creatine phosphokinase in altered thyroid states.' *Journal of Clinical Endocrinology*, 25, 723–31.

Hughes, B. P. (1962). 'A method for the estimation of serum creatine kinase and its use in comparing creatine kinase and aldolase activity in normal and pathological sera.' *Clinical Chimica Acta*, 7, 597–603.

Kerry, R. J., and Orme, J. E. (1972). 'Psychiatric diagnosis and the In-patient Multidimensional Psychiatric Scale.' British Journal Psychiatry. In the press.

Lorr, M., and Klett, C. J. (1967). *Inpatient Multidimensional Psychiatric Scale*. Palo Alto, Calif.: Consulting Psychologists Press.

—— —— (1968). 'Major psychotic disorders.' *Archives of General Psychiatry*, 19, 652–8.

—— —— (1969a). 'Cross-cultural comparison of psychotic syndromes.' *Journal of Abnormal Psychology*, 74, 531–43.

—— —— (1969b). 'Psychotic behavioural types.' *Archives of General Psychiatry*, 20, 592–7.

Meltzer, H. Y. (1968). 'Creatine kinase in serum: abnormality common to acute psychoses.' *Science*, 159, 1368–70.

Meltzer, H., Elkun, L., and Moline, R. A. (1969). 'Serum-enzyme changes in newly admitted psychiatric patients.' *Archives of General Psychiatry*, 21, 731–8.

Meltzer, H. Y., and Moline, R. (1970). 'Muscle abnormalities in acute psychoses.' *Archives of General Psychiatry*, 23, 481–91.

Sorensen, N. S. (1963). 'Creatine phosphokinase in the diagnosis of myocardial infarction.' *Acta Medica Scandinavica*, 17, 725–34.

Wright, N., Clarkson, A. R., Brown, S. S., and Fuster, V. (1971). 'Effects of poisoning on serum enzyme activities, coagulation, and fibrinolysis.' *British Medical Journal*, 3, 347–50.

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