

CK-MB isoenzyme exceeding creatine kinase, a type of macro creatine kinase phenomenon in Thai hospitalized patients, retrospective data from King Chulalongkorn Memorial Hospital*

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Objective : To determine the prevalence, etiology and clinical significance of macro creatine kinase (CK) defined as CK-MB isoenzyme exceeding creatine kinase, in hospitalized Thai patients.

Methods : All data from laboratory requests for total CK and CK-MB in the inpatient unit sent to Clinical Chemistry Unit, Chulalongkorn University Hospital during the year 1999 were studied. Cases where CK-MB exceeded total CK, defined as a type of macro CK phenomenon, were included. Review of the medical records of these inpatients was performed.

Results : From this study, 5 cases with macro CK were detected. There were 4 female and 1 male patients with age ranging from 34 to 70 years old (average age = 54.8 ± 13.5 years old). Diseases of many systems including brain, lung and liver diseases were found to be the causes of macro CK. No deaths were found in this study.

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Conclusion : *Like other previous studies, the prevalence of macro creatine kinase is about 1.5 % and usually found in older female patients.*

Keyword : *Macro creatine kinase*

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วิโรจน์ ไวกานิชกิจ. CK-MB isoenzyme ระดับสูงกว่า creatine kinase, ปรากฏการณ์ macro creatine kinase ชนิดหนึ่งในผู้ป่วยชาวไทย การศึกษาย้อนหลัง ณ โรงพยาบาลจุฬาลงกรณ์. จุฬาลงกรณ์เวชสาร 2546 พ.ย; 47(11): 727 - 34

- วัตถุประสงค์** : เพื่อศึกษาความชุกของปรากฏการณ์ macro creatine kinase (CK) ในรูปแบบที่ CK-MB isoenzyme มีระดับสูงกว่า creatine kinase ในผู้ป่วยในชาวไทย
- วิธีการ** : ทำการศึกษาย้อนหลังจากบันทึกการส่งตรวจ total CK และ CK-MB ในกลุ่มผู้ป่วยใน ณ หน่วยเคมีคลินิกโรงพยาบาลจุฬาลงกรณ์ ในช่วงปีพ.ศ. 2542 ในกรณีที่มี CK-MB มีระดับสูงกว่า total CK ซึ่งจัดได้ว่าเป็นปรากฏการณ์ macro CK ชนิดหนึ่งได้ทำการคัดเลือกไว้เพื่อทำการศึกษาประวัติต่อไป
- ผลการศึกษา** : ได้จำนวนกรณีศึกษาปรากฏการณ์ macro CK จำนวน 5 กรณี โดยเป็นผู้ป่วยหญิง 4 ราย ผู้ป่วยชาย 1 ราย อายุระหว่าง 34 และ 70 ปี (อายุเฉลี่ย = 54.8 ± 13.5 ปี) พบว่าโรคทางสมอง, ปอด และตับเป็นสาเหตุที่เกี่ยวข้องกับการเกิดปรากฏการณ์ macro CK ทั้งนี้ไม่พบผู้ป่วยที่ตายในโรงพยาบาลในกลุ่มผู้ป่วยที่ทำการศึกษานี้
- สรุป** : ความชุกของปรากฏการณ์ macro creatine kinase (CK) ในการศึกษานี้ได้เท่ากับ 1.5 % ใกล้เคียงกับการศึกษาที่ผ่านมา และมักพบปรากฏการณ์นี้ในผู้ป่วยหญิงชรา
- คำสำคัญ** : Macro creatine kinase

Creatine kinase (CK) is an important enzyme in medicine. Determination of levels of total CK and its isoenzymes is a widely used laboratory test in the present day. CK-MB is a frequently requested CK isoenzyme due to its usefulness as a marker of myocardial infarction.

The total CK level and CK-MB isoenzyme level is determined in the laboratory. Sometimes spurious results due to total and partial determination of unknown values can be found.⁽¹⁾ The macro creatine kinase is an interesting cause for aberrant determination for total CK and CK-MB levels. A higher CK-MB level than total CK level result makes the interpretation of results difficult. This extremely excessive CK-MB is known as one form of macro creatine kinase.

This study was performed in order to determine the prevalence, etiology and clinical significance of such cases in hospitalized Thai patients.

Materials and methods

All data on 323 laboratory requests for total CK and CK-MB in the inpatient unit sent to Clinical Chemistry Unit, Chulalongkorn University Hospital during the year 1999 were studied. Both total CK and CK-MB levels in this study were determined by the NAC - activated method (Boehringer Mannheim). The NAC- activated method is an enzymatic based chemical determination. The unknown CK or CK-MB will catalyze the reaction between creatine phosphate and ADP in the reagent to form ATP. The resulting ATP then reacts with glucose in the reagent to provide glucose-6-P. In the last step of the cascade, glucose-6-P will react with NADP in the reagent to produce NADPH. Then NADPH is measured by UV photometry.

Cases where CK-MB exceeded total CK, defined as a type of macro CK phenomenon, were included. Review of medical records of these inpatients was performed.

Table 1. Detail of case with higher CK-MB level than total CK level in this series.

No	Sex	Age (years)	Total CK(U/l)	CK-MB (U/l)	Definite diagnosis	EKG abnormality
1	Female	68	21	22	Temporal lobe epilepsy, cryptococcal meningitis	No
2	Female	70	50	58	Unstable angina, respiratory failure	No
3	Female	56	103	137	Acute pyelonephritis, Cirrhosis,	No
4	Male	34	26	61	Sepsis	No
5	Female	46	38	45	Pulmonary congestion due to congestive heart failure Lobar pneumonia	No

Results

From this study, 5 cases with macro CK were detected. There were 4 female and 1 male patients with ages ranging from 34 to 70 years (average age = 54.8 ± 13.5 years old). The prevalence of the macro creatine kinase was 1.5 % (total requests equaled to 323 tests).

From medical record review, all 5 cases were suspected for acute coronary syndrome, therefore, the blood samples were collected and sent to the laboratory for analysis of total CK and CK-MB. However, the electrocardiogram examinations of all cases showed no evidence of acute coronary syndrome. Hence, they were not diagnosed to have acute coronary syndrome and not performed follow up total CK and CK-MB tests. Baseline details of each case in this series were presented in Table 1. No death case was detected in this study.

Discussion

These cases are examples of problematic cases in total and partial determination of chemical substances in body fluids, resulting in abnormal laboratory results. The sum quantity of components exceeded the total quantity. Interpretation of these abnormal laboratory results was very difficult.

All cases were those in which the CK-MB level exceeded the CK level. Usually an isoenzyme level should not exceed the total enzyme level.⁽²⁾ There must be some error if the isoenzyme level exceeds total enzyme level. What is the reason? Both total CK and CK-MB levels were measured by the same NAC-activated method. But in the total CK determination all forms of CK were measured. Therefore, the quantity of total CK by this method is

implied directly by determination of product of chemical reaction. While CK-MB determination is based on the principle of immunoassay. A specific antibody is used to inhibit the CK-M moiety without affecting the CK-B moiety. In this method, conclusion that CK-B fraction accounts for one half the activity of CK-MB is accepted. The CK-B fraction is determined by the NAC-activated method. The CK-MB level is assumed to be equal to two times the CK-B level. Therefore, the presence of isoenzyme CK-BB may stimulate an increased proportion of CK-MB in the immunologic CK-MB assay. CK-BB can stimulate falsely elevated CK-MB exceeding 35 % and even up to twice the total CK activity. CK-BB can be measured in the serum after damage to many organs such as brain, liver, kidney and lung.⁽³⁻⁴⁾

An atypical CK isoenzyme result, called macro CK,⁽⁵⁾ can be found in 3 - 6 % of hospitalized patient especially in elderly females. In this situation, the total CK is usually in the normal range but a high CK-MB level can be observed. In these patients, the reasons relating to macro creatine kinase are good examples for why CK-MB level exceeds total CK level. The limitation of biochemistry tests for determination of isoenzyme has been discussed. Another alternative method to measure isoenzymes, such as electrophoresis, should be used in these problematic cases.

Macro creatine kinase (Macro CK) is a major cause of elevations of the creatine kinase MB isoenzyme (CK), which may cause mistakes in the evaluation of patients suspected of ischemic cardiopathy.⁽⁶⁻⁸⁾ Its presence in serum interferes with the immunoinhibition methods normally used in emergency room laboratories causing false positive

results in the evaluation of the total creatine kinase level (CK), compared to the CK-MB levels. Usually, the CK-MB activity exceeds total CK activity by more than 25 %.^(6,8 - 10) Increasing concentrations of various types of creatine kinase isoenzymes mimic myocardial infarction or injury.⁽¹¹⁾ Probably a maximum of 1% of patients with suspected acute myocardial infarction,^(11 - 13) have macro CK in concentrations causing diagnostic errors.

Of interest, in Thailand, there had been no reported about the prevalence of macro CK and its clinical correlation among the Thais, therefore, we performed this study. Like the previous studies,^(11 - 13) our study showed that the macro CK was common in elderly female patients, with an approximate prevalence of 1 %. In clinical practice, markedly elevated levels of CK-MB, or increased levels of CK-MB in combination with CK-BB may point away from a myocardial origin and toward the existence of a malignancy. Macro CK can be detected as an abnormal band in creatine kinase electrophoresis. However, in the setting with lack of electrophoresis, the misinterpretation can be performed without the knowledge on macro CK.

In general, macro CK can be distinguished as two types, type I and type II.⁽¹⁴⁾ Presence of both variant CK isoenzymes may lead to diagnostic or therapeutic errors due to an altered CK:CK-MB ratio.⁽¹⁵⁾ The serum total CK is significantly higher, and an increased CK-MB proportion is also significantly more common in patients with macro CK type 1 than in those with type 2. Macro CK types 1 and 2 are much more heat stable than CK-MB and CK-BB, and thus, by heating samples for 20 min at 45 degrees C, the presence of thermostable macro types can be

demonstrated.⁽¹²⁾ In addition, macro CK type 2 has a much higher activation energy than macro CK type 1. The phenomenon described as CK-MB exceeded total CK like in this study is the common presentation of macro CK type II.⁽¹⁶⁾ Although this type of macro CK is not as clinical important as macro CK type I, it is always misinterpretation as laboratory analysis error and resulted in repeated request for retest and also result in unnecessary lost of money.

Nevertheless, like other macro enzymes⁽¹⁷⁾ such as macroamylase and macro lactate dehydrogenase, macro CK type II can be detected in advanced age and malignant lesions.⁽¹⁸⁾ It can be found in diseases of many organ systems such as brain,⁽¹⁹⁾ thyroid,⁽²⁰⁾ GI,^(21 - 22) prostate,⁽²²⁾ breast⁽²²⁾ and kidney.⁽²³⁾ However, macro CK isoenzyme type II in the serum of apparently healthy individuals has also been reported.^(24 - 27) In conclusion, like other previous studies, the prevalence of macro creatine kinase is about 1.5 % and usually found in the old female patients.

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