MAGNESIUM AND ZINC STATUS IN SURVIVORS OF SUDDEN UNEXPLAINED DEATH SYNDROME IN NORTHEAST THAILAND

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Abstract. Sudden Unexplained Death Syndrome (SUDS) is a major health problem in rural residents of Northeast Thailand. The cause of death in SUDS is suspected to be cardiovascular abnormalities. As magnesium (Mg) and zinc (Zn) deficiency contribute significantly to several cardiovascular diseases, we investigated the Mg- and Zn-status of patients with sudden respiratory distress and cardiac arrest who had survived resuscitation attempts or a near-SUDS episode (N-SUDS). The following subjects were enrolled: 12 N-SUDS inhabitants of rural Northeast Thailand (rural group 1, R1), 13 rural villagers with no past history of N-SUDS (rural group 2, R2), 15 urban Northeasterners (urban group 1, U1); 13 Bangkokians (urban group 2, U2). All subjects were free of structural heart disease. Magnesium and zinc were assessed by atomic absorption spectrophotometry of samples of plasma, red blood cells (RBC), white blood cells (WBC), and 24-hour urine. The mean levels of magnesium in the RBC, WBC, and 24-hour urine of N-SUDS patients (R1) were significantly lower than those of the urban groups (U1 and U2), while the plasma levels did not show any differences. When comparing the Zn-status of R1 with that of the urban groups (U1 and U2), the plasma, RBC, and WBC levels were found to be significantly lower in R1 (except for the RBC-Zn of the U1 group), while the 24-hour urine levels was higher. Although the magnesium and zinc parameters were not significantly different between the rural groups R1 and R2, the prevalence of hypomagnesuria (<2.2 mmol/day), hypozincemia (<9.7 µmol/l), and hyperzincuria (>10.7 µmol/day) was higher in the R1 group. These findings suggest that the homeostasis of both magnesium and zinc is altered in N-SUDS patients. Similar alterations, to a lesser degree, were observed in those people living in the same rural environment (R2).

INTRODUCTION

Sudden Unexplained Death Syndrome (SUDS) or Sudden Unexplained Nocturnal Death Syndrome (SUNDS) disproportionately affects the rural population of Northeast Thailand and Southeast Asia (Aponte, 1960; Tatsanavivat *et al*, 1992; Tungsanga and Sriboonlue, 1993). The victims are usually in good health prior

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to the onset of the syncopal attack, which is sudden, only a few minutes long, and suggestive of cardiac arrhythmia. Previous studies of Southeast Asian refugees (Otto *et al*, 1984; Kirschner *et al*, 1986) and a recent study of Thai men who serviced near-SUDS (N-SUDS) (Nadeemanee *et al*, 1997) shown that ventricular fibrillation (VF) was both a possible cause of cardiac arrest and associated with SUDS. Studies of Thai men have demonstrated that SUDS-victims show a characteristic electro-cardiographic pattern of right bundle-branch block (RBBB) and ST elevation in precordial leads (V1-V3), as described in the patients with *Brugada* Syndrome (Nadeemanee *et al*,

1997), a condition that is characterized by spontaneous VF and associated with the sudden death of subjects free of structural heart diseases (Brugada and Brugada, 1992).

Although the Brugada sign, which suggests a genetic defect, was found in SUDS and N-SUDS patients, other precipitating factors must be present to trigger the symptoms of SUDS. These proposed precipitating factors include sex, emotional stress, overwork, and potassium deficiency; these factors are commonly found among the people of rural Northeast Thailand (Sitprija *et al*, 1991; Tosukhowong *et al*, 1996). Other factors, such as magnesium and zinc imbalances, have been noted in sereral cardiovascular diseases (Reunanen *et al,* 1996; Martin-Lagos *et al,* 1997; Songchitsomboon *et al,* 1999; Sasaki *et al,* 2000). The combination of these factors (electrolyte disturbances and Brugada sign) might cause myocardial predisposition in SUDS.

Magnesium, the second most abundant intracellular cation, is a cofactor of a number of enzymes involved in the energy metabolism and biosynthesis of proteins and nucleic acids. It is essential for the maintenance of the intracellular potassium concentration. Magnesium infusions alone can increase muscle potassium and magnesium levels and significantly decrease the frequency of ventricular ectopic beats (Dyckner and Wester, 1987; Dorup *et al*, 1993). These ectopic beats have been attributed to the role of magnesium as a cofactor for Na^+-K^+ ATPase enzyme, which catalyzes the cellular influx of potassium in exchange for sodium (Na) efflux (Garnett and Kemp, 1975).

Zinc is required in trace amounts in the normal diet and has a wide range of important functions. Zinc is a metalloprotein similar to magnesium and is an essential component of more than 300 enzymes, especially those involved in vital cellular processes such as protein, DNA, and RNA biosynthesis (Sandstead, 1986). The plasma level of magnesium and zinc may not reflect the actual whole-body status, while leukocyte magnesium and zinc content are claimed to be more accurate reflectors of the whole-body status and can be used to assess magnesium and zinc deficiency states (Ryzen *et al*, 1985; Brown, 1998). We conducted a study to measure the levels of magnesium and zinc in plasma, red and white blood cells, and 24-hour urine of both N-SUDS and normal subjects.

SUBJECTS AND METHODS

Subjects

Four groups of male subjects were enrolled in our study. Rural group 1 (R1) consisted of 12 survivors of N-SUDS episodes with aged between 25 and 50 (33.5 ± 6.9) years. They were all in good health before the reported N-SUDS syncopal attack and respiratory distress. These subjects were mainly subsistence farmers living in rural Northeast Thailand; all were Thai-Lao ethnic groups and has no past history of drug habituation or addiction. A typical history given by them or their family members was of a sudden syncopal attack, lasting a few minutes, during rest or sleep. It usually occured at night, but not always. Other reported signs and symptoms included nightmare, night terror, groaning or muttering, spastic rigidity or limb contraction, or infrequently, choking or coughing. Forceful shaking, stroking or chest compression was sufficient to resuscitate the subjects.

Rural group 2 (R2) consisted of 13 healthy rural villagers living in the same villages as the R1 subject, aged betwenn 23 and 50 (34.2 ± 6.5) years. Brain magnetic resonance imaging, electrocardiography and electroencephalography (EEG) were negative for both R1 and R2.

Urban group1 (U1) consisted of 15 healthy city dwellers living within the same provinces as the R1 and R1 subject, aged between 22 and 49 (35 ± 7.2) years. They were chosen as the control group since they were Thai-Lao ethnic groups and had no past history of syncopal attacks or family history of SUDS.

Urban group 2 (U2) consisted of 13 healthy personnel from the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, age between 24 and 50 (35.5 ± 8.4) years. They were assigned to another control group as they were Central Thai or Thai-Chinese ethnics groups and had no past history of syncopal attacks or family history of SUDS. R2, U1 and U2 subjects were apparently healthy with normal urinalysis and physical examination.

This study protocol was approved by the Ethics Committees of the Faculty of Medicine at Chulalongkorn University. Each subject gave written informed consent.

Blood

Plasma, WBC, and RBC samples were separated from 10 ml of venous blood drawn from fasting subjects through heparinized tubes and centrifugation at 1,800 rpm for 10 minutes at 4ºC. The plasma was then removed and stored at -20ºC for magnesium and zinc analysis by atomic absorption spectrophotometry. The buffy coat and topmost layer of the RBC were collected and diluted in saline solution. The WBC was separated out by using Ficoll-hypaque (relative density 1.077; Sigma Chemical Co, St Louis, MO, USA) centrifugation in a swinging-bucket rotor. The contaminated RBC were removed after hypotonic lysis by resuspension of the washed cell pellets in 1 ml of deionized water for 1 minute, followed by washing with choline chloride (Alfrey *et al*, 1974). WBC fractions were finally washed and gently re-suspended in isotonic saline solution. The number of cells in the suspension was determined by using a hemocytometer (Bright-Line, Fisher Scientific, Pittsburgh, PA, USA). The remaining cell suspension was stored at -20ºC. The packed RBC were washed three times with isotonic saline solution. The hematocrit and hemoglobin concentrations were assayed by using the Hettich hematocrit and the cyanmethemoglobin techniques respectively. The remaining RBC was suspended in distilled water and stored at -20ºC. Magnesium and zinc concentrations in the WBC were expressed as μmol/10^{10} cells, and in the RBC as μmol/g hemoglobin (Hb). Within-run coefficients of variation in the RBC and WBC (n = 10) were 2.1% and 3.5% respectively for magnesium levels and 1.98% and 3.2% respectively for zinc level.

Urine

Two 24-hour urine specimens from each subject were collected and preserved with thymol solution. All urine specimens were first analyzed for creatinine content by modified Jaffe's reaction. Any urine specimen with a creatinine level of less than 20 mg/kg body weight/day was regarded as improperly collected and discarded. The measurement of urinary zinc and magnesium contents was then performed by atomic absorption spectrophotometry.

Statistical analysis

Data were expressed as the mean ± SD. The statistical significance of the values was determined using SPSS (version 10): *t*-tests, χ^2, ANOVA and multiple-regression correlation analysis. Statistical significance was accorded to a p-value < 0.05.

RESULTS

Mg-status (Tables 1,2)

Plasma Mg-status in all groups was within the normal range and there were no significant differences among the groups. RBC magnesium in R1 and R2 groups was significantly lower than the in the U1 and U2 groups; WBC magnesium showed a similar pattern: significantly lower in R1 and R2 than in U1 and U2. The % hypomagnesumia that was lower than the mean minus 2SD of the 24hr-urine magnesium of the control group (U2; <2.2 mmol/day) was 75 (R1), 61.5 (R2), and 6.6 (U1). The distribution of magnesium levels in the plasma, RBC, WBC, and 24hr-urine of all groups is shown in Fig 1.

Zn-status (Tables 1,2)

Plasma Zn-status in the rural groups was significantly lower than in the urban groups; the same could be said of WBC zinc. When
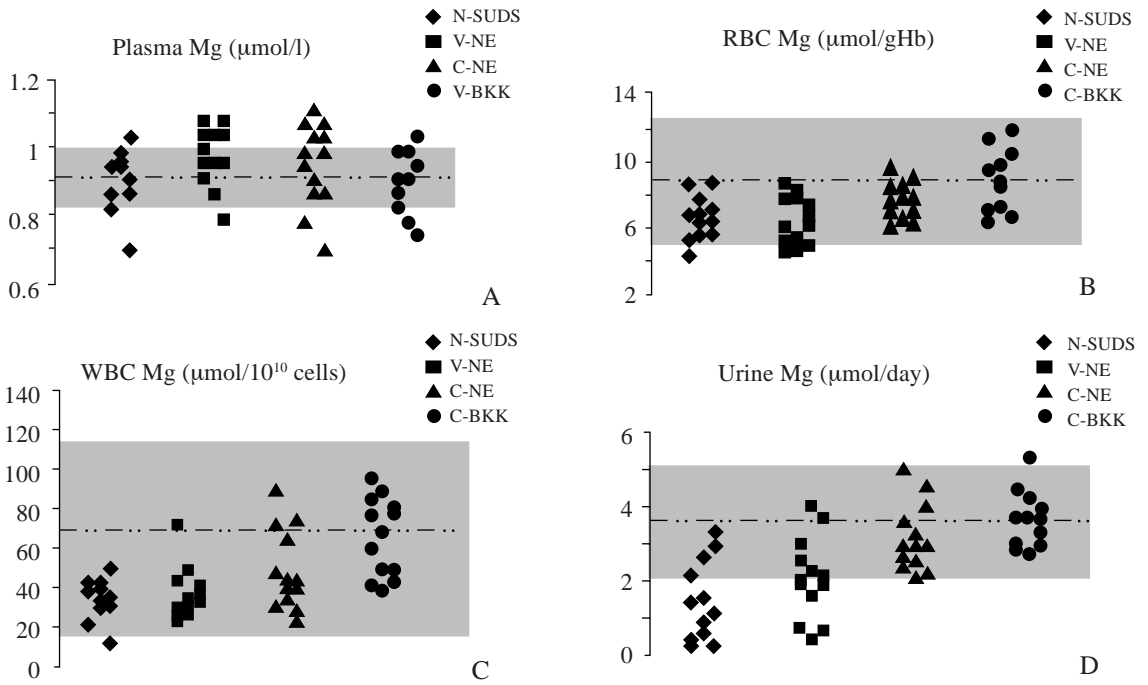
Fig 1–Distribution of magnesium content in plasma (A), RBC (B), WBC (C), and urine (D). NSUDS, V-NE, C-NE and C-BKK are R1, R2, U1 and U2 groups respectively. Values in gray zone represent the values in the range of mean ± 2SDs of the control group (U2).
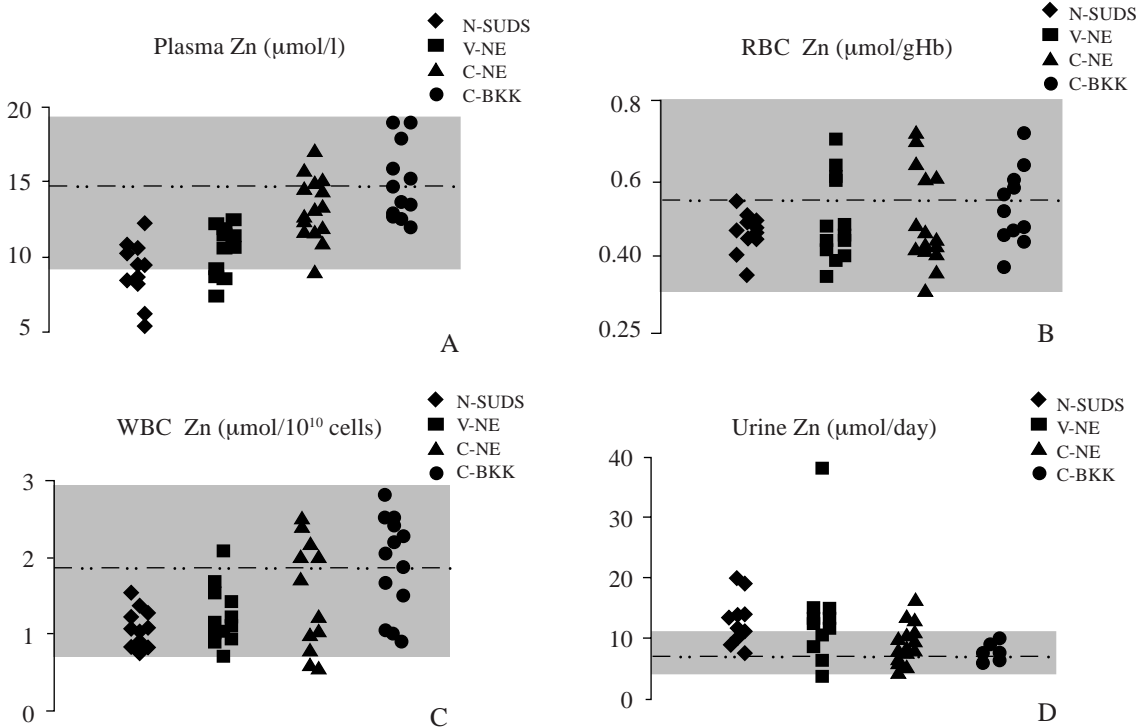

Fig 2–Distribution of zinc content in plasma (A), RBC (B), WBC (C) and in urine (D). NSUDS, V-NE, C-NE and C-BKK are R1, R2, U1 and U2 groups respectively. Values in gray zone represent the values in the range of mean ± 2SDs of the control group (U2).

Table 1

Magnesium and zinc levels in plasma, red blood cells (RBC), white blood cells (WBC) and 24 hr urine samples collected from subjects of R1 (N-SUDS), R2 (Rural Northeasterners, V-NE), U1 (Urban Northeasterners, C-NE) and U2 (Metropolitan Bangkokians, C-BKK).

Parameters	R1 (n = 12)	R2 (n = 13)	U1 (n = 15)	U2 (n = 13)
Magnesium in				
Plasma (mmol/l)	0.90±0.08	0.96±0.09	0.94±0.11	0.90±0.08
% Hypomagnesemia (<0.65 mmol/l)	0%	0%	0%	0%
RBC (μmol/gHb)	6.54±1.30	6.30±1.41	7.54±1.10	8.70±1.80
WBC (μmol/10^{10} cells)	34.0±10.5	35.9±12.9	46.6±19.5	68.0±25.0
24-h-urine (mmol/day)	1.42±1.10	1.82±1.02	3.10±0.86	3.62±0.73
% Hypomagnesuria (<2.2 mmol/day)	75%	61.5%	6.6%	0%
Zinc in				
Plasma (μmol/l)	9.2±2.0	10.3±1.7	13.3±2.1	14.7±2.5
% Hypozincemia (<9.7 μmol/l)	58.3%	38.5%	6.6%	0%
RBC (μmol/g Hb)	0.46±0.05	0.47±0.11	0.50±0.12	0.55±0.13
WBC (μmol/10^{10} cells)	1.09±0.24	1.20±0.37	1.78±0.90	1.90±0.64
24-h-urine (μmol/day)	13.6±3.60	14.0±8.19	10.1±3.20	8.32±1.24
% Hyperzincuria (>10.7 μmol/day)	75%	69%	33.3%	0%

Table 2

Statistical analysis showing p-values of the comparison between groups of the subjects for the values of magnesium and zinc in Table 1.

	p-value					
	R1 *vs* R2	R1 *vs* U1	R1 *vs* U2	R2 *vs* U1	R2 *vs* U2	U1 *vs* U2
Magnesium in						
Plasma	NS	NS	NS	NS	NS	NS
RBC	NS	<0.042	<0.003	<0.016	<0.001	NS
WBC	NS	<0.044	<0.0001	NS	<0.021	<0.020
24 h urine	NS	<0.0001	<0.0001	<0.01	<0.0001	NS
Zinc in						
Plasma	NS	<0.0001	<0.0001	<0.0001	<0.0001	NS
RBC	NS	NS	<0.026	NS	NS	NS
WBC	NS	<0.011	<0.0001	<0.003	<0.02	NS
24 h urine	NS	<0.016	<0.0001	<0.05	<0.028	NS

using the value of the mean -2SD of the plasma zinc of U2 as the lower limit for normal (<9.7 μmol/l), 58.3%, 38.5% and 6.6% in R1, R2 and U1 respectively showed hypozincemia. Intergroup RBC-Zn was not significantly different (expept when comparing R2 with U1). It was found that 24hr-urine zinc in rural groups were significantly higher than in urban groups. The % hyperzincuria that was higher than the mean plus 2SD of the 24hr-urine zinc of the control group (U2; >10.7 mmol/day) was 75 (R1), 69 (R2) and 33.3 (U1). The distribution of zinc in the plasma, RBC, WBC and 24hr-urine of all groups is shown in Fig 2.
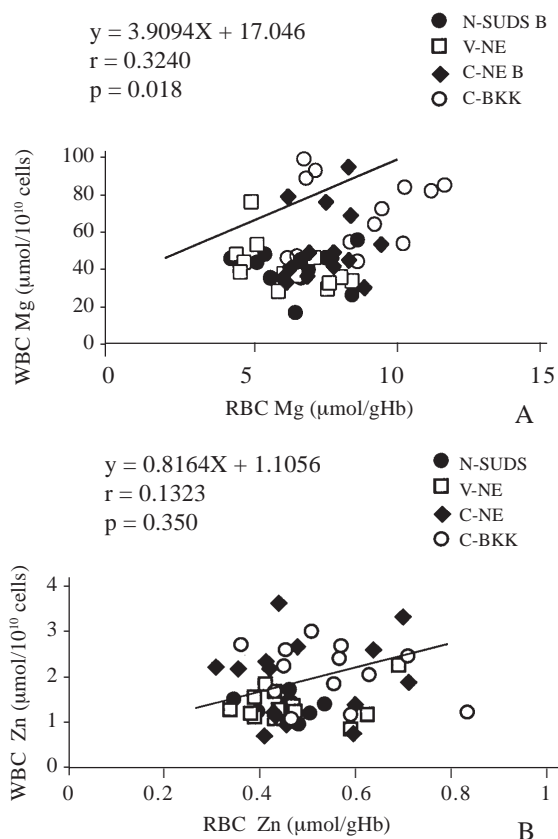
$y = 3.9094X + 17.046$
$r = 0.3240$
$p = 0.018$

● N-SUDS B
□ V-NE
◆ C-NE B
○ C-BKK

WBC Mg (μmol/10^{10} cells)

RBC Mg (μmol/gHb)

A

$y = 0.8164X + 1.1056$
$r = 0.1323$
$p = 0.350$

● N-SUDS
□ V-NE
◆ C-NE
○ C-BKK

WBC Zn (μmol/10^{10} cells)

RBC Zn (μmol/gHb)

B

Fig 3–Linear regression of WBC-Mg and RBC-Mg (A) and WBC-Zn and RBC-Zn (B) from 4 groups of subjects. NSUDS (●), V-NE (□), C-NE, (◆)and C-BKK (○) are R1, R2, U1 and U2 groups respectively.

Correlation between RBC-Mg and WBC-Mg (Fig 3A)

There was significant correlation between RBC-Mg and WBC-Mg ($r = 0.3240$; $p = 0.018$).

Correlation between RBC-Zn and WBC-Zn (Fig 3B)

There was no significant correlation between RBC-Zn and WBC-Zn ($r = 0.1323$; $p = 0.350$).

DISCUSSION

It is accepted that the true body Mg-status can be determinated by the magnesium loading test, the gold-standard method which, although somewhat cumbersome, can be used in subjects with renal insufficiency (Ryzen *et al*, 1985; Whang, 1987). Alternative practicable determinations of Mg-status include those that measure the intracellular magnesium of erythrocyte, lymphocyte or leukocyte (Whang, 1987; Ryan, 1991; Rocchi *et al*; 1994; Brown, 1998). In the present study we found that the intracellular magnesium levels of the erythrocytes and leukocytes of the control group (U2) were similar to those previously reported; the rural groups' (R1 and R2) subjects were affected by RBC- and WBC-Mg deficiency to a greater extent than subjects from the urban groups (U1 and U2); notably, the R1 (N-SUDS) group was the worst affected. In addition, we found a correlation between RBC- and WBC-Mg which had not been found in a previous study (Elin, 1987). Total plasma-Mg was not significantly different among the groups, suggesting that it has poor discriminative value as an indicator of Mg-status, as reported elsewhere (Alfrey *et al,* 1974; Sasaki *et al*, 2000).

Magnesium deficiency had been shown to be associated with cardiac arrhythmias, since magnesium blocks the cellular efflux of potassium through potassium channels in cardiomyocytes and also acts as a cofactor of Na^+, K^+-ATPase. Depletion of magnesium may lead to excessive cellular efflux of potassium, impaired potassium influx and a reduction of the intracellular potassium content, leading to depolarization of the cardiomyocytes. Magnesium deficiency and Na^+, K^+-ATPase pump deactivation may be implicated as potential contributors to cardiac arrhythmias.

Plasma and serum zinc have been widely used as the indices for body Zn-status because of the convenient techniques and reliable results for whole body storage determination (Lekalis and Kalofoutis, 1980; Brown, 1998). Mixed lymphocyte/leukocyte-Zn concentration is more reliable due to their short cellular lifespan (Rocchi *et al*, 1994). Our findings of plasma-Zn of the urban groups were similar to those previously reported in Thailand (Songchitsomboor *et al*, 1999). The average

levels of plasma-, RBC- and WBC-Zn were lower in the rural groups, especially in the R1 group, suggesting that these subjects had not only low zinc but also low magnesium.

There are many reports suggesting that zinc is one of the trace elements that might counteract the development of cardiovascular disease (Houtman, 1996); a significantly decreased serum zinc concentration is found in many fatal cardiovascular diseases (Martin-Lagos *et al*, 1997; Songchitsomboon *et al,* 1999). Reunanen *et al* (1994), reported that significantly low serum zinc and high serum copper were associated with an increased mortality in all cardiovascular diseases.

In Northeast Thailand, 80% or more of total daily energy intake comes from glutinous rice diets (Dinning, 1974; Sriboonlue *et al,* 1998a,b), which are low in potassium, magnesium and zinc. In addition, many foods commonly eaten by people in Northeast Thailand contain high phytate, an inhibitor of magnesium and zinc absorption (Oberleas and Harland, 1981; Boontaveeyuwat *et al,* 1990). We conclude that a diet with insufficient potassium, magnesium and zinc is the most important cause of deficiency in the people of this region.

Although some survivors of N-SUDS and some relatives of SUDS victims from Northeast Thailand had documented VF as a characteristic ECG pattern of Brugada syndrome (Sangwatanaroj *et al,* 2001), this characteristic marker is merely the underlying cause: a tendency that must be aggravated by other precipitating factors to result in SUDS symptoms. In this study, we found that N-SUDS patients (R1 group) have greater magnesium and zinc deficiency than those of other groups, including the non-SUDS rural dwellers (R2 group). We suggest that magnesium and zinc deficiency might be precipitating factors that reinforce intracellular potassium deficiency in cardiomyocytes, thereby inducing cardiac arrhythmia or SUDS in people from Northeast Thailand who have a positive Brugada sign.

We suggest that supplementary potassium, magnesium and zinc for high risk groups may prevent cardiac arrhythmia and SUDS events. a suggestion requiring further study.

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