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Hypophosphatemia in generalized tonic-clonic seizures: a cohort analysis

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Abstract

Transient loss of consciousness (LOC) is very common issue. Syncopes and generalized tonic-clonic (GTC) seizures are common causes mostly differentiated by history. Several laboratories serum markers (mostly creatine kinase and lactate) can be helpful especially when history is unreliable. We explore the potential supporting role of electrolytes plasma level in that setting.

We retrospectively collected 178 consecutive episodes of loss of consciousness in adults from the EEG database of our hospital (CHUV, Lausanne) seen over 3 years in our emergency department. Plasma level of the different electrolytes (sodium, potassium, phosphate, calcium, magnesium) were recorded as well as basic demographics, diagnosis, blood sample delay and history of alcohol abuse.

We analysed 128 episodes with sufficient documentations (7 had uncertain diagnosis): we compared electrolytes values between GTC seizures (75 episodes) and other LOC, (46 episodes). Phosphate and calcium levels were associated with GTC seizures; median=0.79 (range 0.34-1.37) vs 0.93 mmol/l (range 0.52-1.56) p=0.001 for phosphate and median= 2.32 (range 1.92-2.53) vs 2.27 mmol/l (range 2.0-2.53) p=0.03 for calcium. Considering abnormal values, only hypophosphatemia (94% of abnormal phosphate level) was associated with GTC seizures with 37 (51 %) abnormal phosphate in GTC seizures and 15 (33%) in other LOC (p=0.02, Chi squared), independently from blood sampling delay, alcohol abuse and other electrolytes level. Hypophosphatemia below 0.6 mmol/L was 93% sensitive and 85% specific of GTC seizure. Hypophosphatemia was self-limited.

Our data suggest that transient hypophosphatemia is common after GTC seizures. This hypophosphatemia is unlikely to be causing the seizure, but is rather a consequent intracellular shift. Phosphate level could be another biological marker helping differentiate GTC seizures from other LOC, especially when history is unclear. Timing of the blood sample

should be taking into account in its interpretation. A prospective study is needed to confirm these findings.

Introduction

Loss of consciousness (LOC) is a common cause of admission in emergency departments accounting for 1 in 20 admissions[1]. Assessing the nature of the episodes mostly rely on history taking and clinical examination[2], half of these episodes are diagnosed as generalised tonic-clonic (GTC) seizures[3]. There are currently no gold standard paraclinical examination distinguishing syncopes from convulsive seizures. A blood sample is routinely performed in case of suspicion of an epileptic seizure as part of the etiological work-up[4]. GTC seizures induce plasma changes can be used to help assessing transient LOC, when history and clinical examination are unyielding.

Seizures are long known to induce systemic changes such as plasma prolactin[5-8], creatine kinase (CK) (typically with a few hours delay)[6, 9-11], lactate [12, 13], ammonium[14, 15] adrenocorticotropic hormone (ACTH) [16] and cortisol increases[8, 16]. Other studies also suggested serum growth hormone (GH) levels increase[17], but not consistently[16]. Several of these studies also assessed prolactin [6, 17, 18] , lactate[19] or CK [6, 10] increase as markers mostly to differentiate GTC seizure versus non epileptic psychogenic seizures or syncopes. Some of these markers (such as prolactin) allow mostly the differentiation between GTC seizures and syncopes versus psychogenic non epileptic attacks[20]. Recently seizure were also found to be associated with an increase of multiple inflammatory parameters[12]. Except lactate, CK and ammonium, other markers are seldom used in clinical practice to assist the diagnosis of transient LOC as these tests are uncommonly available in emergency settings.

In our centre, when an epileptic seizure is part of the differential diagnosis, a full electrolytic work-up (including calcium, magnesium, phosphate) is performed. We observed that abnormal phosphate level was not uncommonly found in patients assessed in that setting. The aim of this study was to assess the value of plasma electrolytes levels in the assessment of transient LOC whether this could represent another help for diagnose GTC seizures from others causes of transient LOC.

Methods

This study was approved by our local ethic committee, and the need to consent was waived given the fully retrospective nature of the study.

We identified all consecutive episodes of transient LOC from the EEG reports database of our hospital (CHUV, Lausanne) using the following keywords: “syncope”, “fainting”, “consciousness”, “loss”, “seizure”, “convulsions”, “tonic-clonic” in the period between 01.01.2014 and 31.12.2016. We included only adult patients (at least age 18 on the day of the hospital admission). For each episode, we recorded the following data from electronic medical notes: gender; age; diagnosis at discharge (based on discharge summary); as well as history alcohol/toxic abuse. Laboratory value (in mmol/l) for plasma sodium, potassium, phosphate, total calcium and magnesium level were recorded; delay between the event and blood samples were also recorded. When follow-up was available for these laboratory values, it was also recorded.

Statistical analyses were performed using SPSS version 25 (IBM inc.). Chi square, Fisher’s exact test, Mann-Whitney tests were used as needed for univariable analyses. Receiver operating characteristic (ROC) was used to assess sensitivity and specificity for a change. Backward multiple regression were used to correct for potential confounders (such delay between event and blood test, alcohol abuse) and assess the predictor value of all electrolytes considered together.

Results

We identified 187 episodes, we excluded 59 cases whose documentation was incomplete. Among the 128 episodes left, there was 126 patients (2 people had 2 episodes). All demographic data can be found in table 1. The diagnoses at discharges can be summarised as follows: 75 episodes were diagnosed tonic-clonic seizures (58.6%), 25 were syncopes (19.5%), 11 were focal seizures with loss of awareness (8.6%), 10 were other diagnoses (psychogenic non-epileptic attack, acute confusional state, concussion, hyperventilation episode) (7.9%) and 7 unclear episodes for which the possibility of general tonic-clonic seizure could not be determined (5.5%).

We then differentiated between GTC seizures and other LOC (the seven episodes with uncertain diagnosis were not included in these analyses). There was no significant difference in demographic terms between GTC seizures and other LOC (details are shown in table 1). There was a significantly shorter delay in blood samples for the GTC seizures in comparison to other LOC episodes (median 1.7h vs 2h, p=0.003, Mann-Whitney) and greater prevalence of alcohol abuse in GTC seizures (10% vs 0%, p=0.03, Fisher's exact). Electrolytes changes in GTC seizures and other losses of consciousness episodes are shown in figure 1. Considering electrolytes level values, phosphate and calcium were independently associated with GTC seizures; median=0.79 (range 0.34-1.37) vs 0.93mmol(l (range 0.52-1.56) p=0.001 for phosphate and median= 2.32 (range 1.92-2.53) vs 2.27mmol/l (range 2.0-2.53) p=0.03 for calcium. Considering abnormal values, only phosphate values were associated with seizures, with 37 (51 %) abnormal values in GTC seizures in comparison with 15 (33%) in other LOC episodes (p=0.02, Chi squared). The vast majority of abnormal phosphate levels was a decreased below 0.8 mmol/L (47 of 50, 94%) while only 3 (6 %) were increased above 1.4mmol/l. None of the seizures or other LOCs was considered as being caused by hypophosphatemia. We searched in the 10 most severely low phosphatemia for the use of diuretic medication, but we did not find any.

Hypophosphatemia was the only variable independently associated with the diagnostic of GTC seizure when correcting for delay in blood sample, other electrolytes, alcohol abuse, age, and gender. The presence of abnormal hypophosphatemia increased the chance of diagnosing GTC seizure by 2.5 fold (95% CI: 1.5-5.6, p=0.02), when correcting for abnormal calcium (as there was a trend toward higher calcemia in GTC seizures), this effect increased (OR: 3.2, 95% CI: 1.34-7.6, p=0.008). Using ROC, phosphate level below 0.6 mmol/L was associated with 93% sensitivity and 85% specificity for diagnosis of GTC seizure. Finally when comparing GTC seizures and focal seizures, somewhat higher proportion of hypophosphatemia was found in GTC (37, 51%) than in focal seizures (4, 40%), but this did not reach significance.

There was significant correlation (p=0.01, two tailed Pearson) between the delay of blood sampling and phosphate level, which tend to normalise with the sample delay increasing. Phosphate levels were higher after the median delay of blood sampling (2hours) compared to

earlier, (median phosphatemia level was 0.8mmol/L; range: 0.35-1.34 before the median sampling delay versus 0.95; range: 0.34-1.35 after the median sampling time). In three cases, patients with initial hypophosphatemia had several sequential follow-up levels as follow-up; 2 of them normalized (0.66 to 1.16 in 2h 10minutes and 0.64 to 1.3mmol/l in 1 hour), while the third one showed no normalisation (0.5 to 0.47mmol in 7 hours) in a context of alcohol abuse.

Discussion

Electrolytes abnormalities are common in patients investigated for transient LOC; laboratory showed abnormalities in more than half of the episodes. Phosphate abnormalities were the most common and showed a differential distribution according the established diagnosis. Namely, hypophosphatemia was seen in every second GTC seizure and less commonly in other LOC episodes. This significant association was not explained by confounders such as differential delay in blood sampling (GTC seizure had understandably short delays), alcohol abuse (with its risk of poor nutrition) or use of diuretics (which can lead to renal loss of phosphate).

Hypophosphatemia can conceivably be considered as the cause of the diagnosed seizure. Disturbance of phosphate plasma level are however not recognized as a cause of provoked seizures[21], cases of seizure associated with hypophosphatemia were indeed rarely reported, and generally associated with other disturbances (refeeding syndrome and mechanical hyperventilation in intensive care unit) [22-24]. In the series reported here, hypophosphatemia was not considered as the cause of the episodes. The time course of phosphate levels as well as the few follow-up data also suggest a transitory self-limited phenomenon.

Our data suggest that hypophosphatemia is rather a consequence of GTC seizures than its cause. The tendency of hypophosphatemia to normalise over a few hours spontaneously suggests a redistribution mechanisms rather than a loss through renal excretion for instance. There are several explanations to this phenomenon that could be the consequences of a physiological stress. Indeed, it is known that stress hormones such as epinephrine or glucagon can lead to electrolytes redistribution, and especially considerable intracellular phosphate

shifts[25, 26]. Intense efforts have also been found to cause PTH variation which leads to transient hypophosphatemia[27]. Hypophosphatemia in a setting of transient LOC could therefore hint a peak of stress hormones and sustained muscular activity during the course of the episode.

Plasma hypophosphatemia following an episode of LOC could therefore represent a biomarker and consequently a diagnostic help to clarify the nature of such episode. In our study, presence of hypophosphatemia was associated with a 2.5 fold increased chance of diagnosing a convulsive seizure. Phosphate concentration in blood samples collected after a LOC could be useful in clinical practice to assess the likelihood of a GTC seizure episode, especially in absence of history, especially when phosphatemia is below 0.6 mmol/l. In terms of sensitivity and specificity, the value of hypophosphatemia seems roughly similar to other established markers[28]. For CK, an elevation of > 15 U/l is helpful distinguishing GTCs from syncope with a sensitivity of 69% and a specificity of 94% [29], while a threshold of 2.3 mmol/l for lactate level is associated with 73% sensitivity and 97% specificity [30] for GTC seizures vs other LOCs. A cut-off of 65 µg/dl for ammonium at arrival at the emergency room could help differentiating GTCs from other cause of LOC with a poorer sensitivity (53%) but a specificity of 90%[31]. Hypophosphatemia (especially in absence of abnormal calcium level) could provide an additional clue in the assessment of transient LOC to differentiate between GTC seizures and other LOC such as syncope. The delay between the event and the blood sample must also be taken into account as our results suggest this is self-limited phenomenon that is likely to subside spontaneous in most case over the hours following the LOC.

Our study has limitations. The retrospective design has several consequences. It may lead to a selection bias as we selected patients from a neurological point of view (all episodes were identified by their EEG recording) and as such there was at least an initial doubt about a potential epileptic seizures in these episodes. We had therefore probably less clear-cut syncope that would have not needed neurological investigation. One advantage of such approach is that all episodes were comprehensively assessed by consulting neurologists, making the diagnosis of GTC seizure as reliable as possible. The syncopes explored here are also those leading to diagnosis difficulties possibly associated with myoclonic jerks. There could be also be an information bias as the treating physician was aware about the abnormal

phosphate level before establishing the diagnosis. We cannot therefore exclude that abnormal electrolytes may have influenced the treating physician in case of uncertainty to consider a diagnosis of epileptic seizure rather than a syncope. In no cases, was however abnormal phosphate level reported as a triggering factor or a cause of the episode. Focal seizures were considered with other episodes, as motor manifestations can widely vary in those seizures, but are most commonly less marked than in GTC seizures. Focal seizure tended to be associated with lower proportion of abnormal phosphatemia, but the limited sample size precludes any conclusion.

A basic limitation of all studies relying on a diagnosis of seizure is the absence of a gold standard diagnostic procedure; the diagnosis is therefore based heavily on history taking. This limitation highlights that biological potential biomarkers should be interpreted together with the episode description as these markers were established in the first place based on clinical data (mostly history). The usefulness of these markers (phosphate level possibly among them) could be situations where no description of the LOC is available.

In conclusion, hypophosphatemia is commonly (51%) found following GTC seizures, this more often than following others LOC such as syncopes. Hypophosphatemia below 0.6mmol/l seems reasonably sensitive and specific to suggest a GTC seizures and it could be therefore used a diagnostic help especially when history is not available. A prospective study is needed to confirm these findings, together with other established markers of seizures.

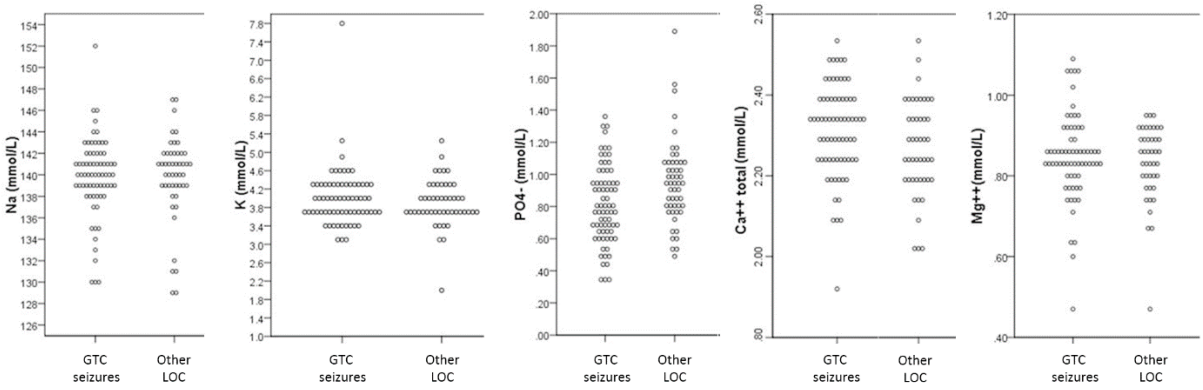

Figure 1 legend: Distribution of plasma electrolytes for sodium, potassium, phosphate, calcium and magnesium (mmol/l) in GTC seizure and in other LOC episodes. Phosphate and total calcium showed both a significant distribution between GTC seizures and other LOC; median 0.79, range 0.34-1.37 in GTC seizure vs median=0.94, range 0.52-1.89 in other LOC for phosphate (p=0.007, Mann-Whitney) and median=2.32, range 1.92-2.53 vs median=2.27, range 2-2.53 (p=0.03, Mann-Whitney) for calcium. Both decreased phosphatemia (OR: 0.04, 95% CI: 0.29-0.007, p=0.001) and increase calcemia (OR:57, 95% CI: 1.3-2432, p=0.03) were independently associated with GTC seizures. Na, K, and Mg showed no different distribution for GTC seizure.

	All n= 128	GTC seizures n= 75	Others LOC n= 46	Test	p
Age	Median: 48 Range: [18-90]	Median: 43 Range: [18-86]	Median: 50 Range: [19-90]	Mann-Withney	0.52
Genre (F)	51 (40%)	29 (39%)	21 (46%)	Chi^2	0.45
History of alcohol abuse	10 (8%)	8 (11%)	0	Fisher's exact	**0.03**
Delay of the blood sample	Median: 2 h Range: 6 min-20h	Median: 1.7h Range: 6 min-17h	Median: 2h Range: 0.5h–20h	Mann-Withney	**0.003**
Abnormal Na	16 (13%)	8 (11%)	8 (17%)	Chi^2	*0.43*
Abnormal K	19 (15%)	10 (14%)	9 (20%)	Chi^2	*0.98*
Abnormal PO4	52 (41%)	37 (51%)	15 (33%)	Chi^2	**0.02**
Abnormal Ca	12 (9%)	5 (7%)	16 (35%)	Fisher's exact	0.11
Abnormal Mg	5 (4%)	4 (6%)	1 (2%)	Fisher's exact	0.65

Table 1 legend

Demographic characteristics and abnormal electrolytic plasma levels in whole series, in GTC seizures and others LOC. Significant p values are in bold.

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