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**LETTER**

# Hypophosphatemia as a key factor in sudden infant death syndrome (SIDS)?

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Dear Sir,

Sudden Infant Death Syndrome or SIDS remains an important cause of mortality in infants. The 2011 publication of Siren and Siren (1) and the subsequent letter to the editor (2) focus on critical diaphragm failure as a possible cause and provide plausible evidence. However, these articles do not explore the metabolic basis for this critical diaphragm failure. Several authors, including Aubier et al. (3) and Fiaccadori et al. (4) have described that the diaphragm is extremely susceptible to hypophosphatemia, and this may be the origin of the symptoms reported by Siren and Siren. Hence, it may well be the yet unexplored underlying mechanism responsible for SIDS.

A reason for suspecting hypophosphatemia as the cause for SIDS is because neonates are extremely prone to developing hypophosphatemia as shown in numerous publications (e.g. (5-8)). A very brief period of stress, like separation from the mother or a brief period of illness, can result in phosphaturia severe enough to result in the loss of 50% of the free phosphate pool within 24 hours. This results in an immediate drop in blood phosphate levels. Worse, this hypophosphatemia can subsequently become aggravated over the course of 1–2 weeks without obvious visible symptoms and despite resumption of normal eating behavior, something not reported in older subjects. In infants with risk factors for SIDS like intrauterine growth retardation, exposure to cigarette smoke, male sex, and heat stress, this phosphaturetic stress response is enhanced possibly through augmented or longer-lasting sympathetic activity (9,10), and, hence, they are more prone to develop severe hypophosphatemia and ATP deficiency.

Hypophosphatemia not only affects contraction of the diaphragm, but it is also involved in the formation of 2,3-diphosphoglycerate (2,3-DPG; more correctly referred to as 2,3-bisphosphoglycerate) in erythrocytes. This 2,3-DPG regulates the release of oxygen from hemoglobin. Tissues with a high metabolic activity result in high levels of 2,3-DPG in the blood causing the liberation of oxygen (11-13). Hypophosphatemia impedes the formation of 2,3-DPG, which subsequently prevents the release of oxygen from hemoglobin and, in effect, suffocates the tissue. Thus, severe hypophosphatemia results in signs of asphyxiation despite adequate access to free air (14), either through inducing an ATP deficiency affecting the diaphragm or through inhibiting oxygen release from hemoglobin. For example, in briefly stressed subjects, in parallel with the drop in plasma phosphate, a doubling of the ratio of $pCO_2/pO_2$, an increase in $SpO_2$, and lactic acidosis were observed but without obvious visible signs of distress. If severe enough, this could lead to death from inner suffocation (SIDS). The presence of fetal hemoglobin may also play a role in SIDS. Fetal hemoglobin purportedly has a higher binding affinity for oxygen (15) and thus could predispose an infant to SIDS when 2,3-DPG is compromised.

Other symptoms of SIDS can also be explained by hypophosphatemia. Hypophosphatemia can lead to petechiae: minor hemorrhages caused by platelet dysfunction (16,17) and often seen postmortem in SIDS victims. Similarly, pulmonary edema (18) has been linked to hypophosphatemia, as have cardiac arrhythmias (19,20). Hypophosphatemia is also implicated in

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the morbidity and mortality associated with refeeding syndrome (21) and in hypophosphatemic rickets, which is more prevalent in boys (22) in line with a higher incidence of SIDS in boys.

Siren and Siren's (1) comment that REM sleep inhibits intercostal muscles compounded by diurnal rhythms in blood phosphate could explain why SIDS strikes during night-time REM sleep. Also, phosphate has a seasonal rhythm with lows in the winter which could explain a higher prevalence of SIDS in this season, and 2,3-DPG is lower in infants exposed to cigarette smoke which could explain a higher incidence of SIDS in houses of smokers (23,24).

In summary, both the etiology as well as the symptoms of SIDS can be explained by hypophosphatemia. A brief stressor can induce hypophosphatemia in infants, particularly in those with SIDS risk factors, and aggravate it despite resumption of normal food intake. This since the urinary loss of phosphate induced by stress or a large drop in metabolic rate and the subsequent enhanced phosphate demand for restarted anabolic processes cannot be quickly compensated by normal dietary intake. This hypophosphatemia can aggravate to the point of affecting $O_2$ release from red blood cells through a depletion of 2,3-DPG or affect diaphragm contractility through ATP deficiency, either one which leads to death from apparent suffocation: SIDS.

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## References


1. Siren PMA, Siren MJ. Critical diaphragm failure in sudden infant death syndrome. Ups J Med Sci. 2011;116:115–23.
2. Siren P. The SIDS-critical diaphragm failure hypothesis revisited. Ups J Med Sci. 2013;118:62–4.
3. Aubier M, Murciano D, Lecocguic Y, Viires N, Jacquens Y, Squara P, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med. 1985;313:420–4.
4. Fiaccadori E, Coffrini E, Fracchia C, Rampulla C, Montagna T, Borghetti A. Hypophosphatemia and phosphorus depletion in respiratory and peripheral muscles of patients with respiratory failure due to COPD. Chest. 1994;105:1392–8.
5. Loudenot A, Michot C, Alberti C, Armoogum P, Tsapis M, Dauger S. High prevalence of hypophosphatemia at PICU admission in non-malnourished children. Intensive Care Med. 2010;36:1443–4.
6. De Menezes FS, Leite HP, Fernandez J, Benzecry SG, de Carvalho WB. Hypophosphatemia in children hospitalized within an intensive care unit. J Intensive Care Med. 2006;21:235–9.
7. Kalan G, Derganc M, Primožič J. Phosphate metabolism in red blood cells of critically ill neonates. Pflugers Arch. 2000;440:R109–11.
8. Antachopoulus C, Margeli A, Giannaki M, Bakoula C, Liakopoulou T, Papassotiriou I. Transient hypophosphataemia associated with acute infectious disease in paediatric patients. Scand J Infect Dis. 2002;34:836–9.
9. Body J, Cryer P, Offord K, Heath H. Epinephrine is a hypophosphatemic hormone in man. Physiological effects of circulating epinephrine on plasma calcium, magnesium, phosphorus, parathyroid hormone, and calcitonin. J Clin Invest. 1983;71:572–8.
10. Deixler E. Sudden infant death syndrome (SIDS) caused by ATP-depletion following hyperventilation, tissue-hypoxia and hypermetabolism – a hypothesis. Z Geburtshilfe Neonatol. 2009;213:122–34.
11. Charache S, Grisolia S, Fiedler AJ, Hellegers AE. Effect of 2,3-diphosphoglycerate on oxygen affinity of blood in sickle cell anemia. J Clin Invest. 1970;49:806–12.
12. Goodford PJ, Norrington FE, Paterson RA, Wootton R. The effect of 2,3-diphosphoglycerate on the oxygen dissociation curve of human haemoglobin. J Physiol. 1977;273:631–45.
13. Young JA, Young MD, Marshall A, Lichtman MD, Cohen J. Reduced red cell 2,3-diphosphoglycerate and adenosine triphosphate, hypophosphatemia, and increased hemoglobin-oxygen affinity after cardiac surgery. Circulation. 1973;47:1313–18.
14. Moran JL, Solomon PJ, Ay Yeung KW, Pannall PR, John G, Eliseo A. Phosphate metabolism in intensive care patients with acute respiratory failure. Crit Care Resusc. 2002;4:93–103.
15. Cochran-Black DL, Cowan LD, Neas BR. The relationship between newborn hemoglobin F fractions and risk factors for sudden infant death syndrome. Arch Pathol Lab Med. 2001;125:211–17.
16. Berner YN, Shike M. Consequences of phosphate imbalance. Ann Rev Nutr. 1988;8:121–48.
17. Knochel JP. Hypophosphatemia. West J Med. 1981;134:15–26.
18. Darsee JR, Nutter DO. Reversible severe congestive cardiomyopathy in three cases of hypophosphatemia. Ann Intern Med. 1978;89:867–70.
19. Schwartz A, Gurman G, Cohen G, Gilutz H, Brill S, Schily M, et al. Association between hypophosphatemia and cardiac arrhythmias in the early stages of sepsis. Eur J Intern Med. 2002;13:434.
20. Venditti FJ, Marotta C, Panezai FR, Oldewurtel HA, Regan TJ. Hypophosphatemia and cardiac arrhythmias. Miner Electrolyte Metab. 1987;13:19–25.
21. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition. 2001;17:632–7.
22. Haider N, Nagi AG, Khan KM. Frequency of nutritional rickets in children admitted with severe pneumonia. J Pak Med Assoc. 2010;60:729–32.
23. Hunt CE, Hauck FR. Sudden infant death syndrome. CMAJ. 2006;174:1861–9.
24. Ditzel J, Lervang H-H. Lifestyle diseases and cardiovascular risk factors are interrelated to deficiencies of major substrates in ATP synthesis. Vasc Health Risk Manag. 2010;6:829–36.