Acute life threatening events associated with hypocalcemia and vitamin D deficiency in early infancy. *A single center experience from the Kingdom of Saudi Arabia*

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Current clinical and epidemiological observations reveal that vitamin D deficiency is not an uncommon health problem, and in the majority of cases the principal cause is nutritional deficiency. It is a preventable condition if adequate intake is achieved through oral supplementation and adequate sunlight exposure.[1] Specific risk factors include lack of maternal-infant vitamin D supplementation and sunlight exposure, traditional skin-covered dress wear, reduced calcium intake during pregnancy, and a sedentary lifestyle.[1] The spectrum of early clinical manifestations range from the common finding of infantile rickets to the occurrence of serious and acute life threatening events (ALTE) such as severe apnea and status epilepticus. Presentation in the form of ALTEs that require pediatric intensive care unit (PICU) admission for cardiorespiratory monitoring and support are rarely reported. A high index of suspicion is therefore essential to avoid potentially drastic consequences of this disease. The main aim of our study was to explore the extent of vitamin D deficiency as a potential cause for ALTE in Saudi infants who were admitted to the PICU via the emergency room. Secondary objectives were to define risk factors and discuss preventive and evidence based treatment strategies to address this often silent and yet potentially serious disease.

A retrospective study was conducted at Doctor Soliman Fakeeh Hospital in Jeddah, Kingdom of Saudi Arabia. The medical records of infants under the age of 12 months were reviewed from January 2007 to January 2009. Data on all infants admitted to the PICU through the emergency room with a clinical diagnosis of ALTE, defined as "an observed frightening episode characterized by some combination of apnea, color change (usually cyanotic or pallid), marked change in muscle tone (usually marked limpness), choking, or gagging" were collected. Infants found to have vitamin D deficiency defined as a serum 25-hydroxyvitamin D 25(OH)-D concentration below 20 ng/ml (50 nmol/L),[1] were included in the study. Vitamin D levels below 5 ng/mL (12.5 nmol/L) were defined as severe deficiency.[1] Infants on anti-convulsant therapy and those with hepatic or renal disease, hypoparathyroidism, a previous diagnosis of seizures, developmental delay and non-nutritional forms of rickets were excluded. Demographic data were extracted and analyzed including: age at diagnosis, gender, race, sunlight exposure, presenting symptoms and signs, detailed physical examination, feeding practice (breast feeding and/ or formula), biochemical profile including serum calcium (Ca^{++}), phosphorus (PO_4), alkaline phosphatase (ALP), parathyroid hormone (PTH) concentration, 25(OH)-D and radiological findings. In addition, maternal data were also collected on life style, sun exposure, and vitamin D supplementation during pregnancy and lactation. The study was approved by the ethics committee of the institution.

Twenty-five infants were diagnosed with ALTE over the 2 years study period. Five (20%) infants admitted with ALTE were diagnosed with vitamin D deficiency. Of the remaining 20 infants, 5 (20%) had gastro-esophageal reflux disease; 5 (20%) febrile seizures; 5 (20%) non-febrile seizures; one (4%) dilated cardiomyopathy; one (4%) bronchiolitis; one (4%) hypoparathyroidism, and 2 (8%) were of unknown etiology. All infants required initial resuscitation in the emergency room and required PICU admission (2-7days) together with close cardio-respiratory monitoring. All infants had an initial workup for ALTE, which involved a complete blood count, biochemical investigations including a screen for metabolic disorders, a full septic work-up inclusive of blood culture, lumbar puncture, naso-pharyngeal aspirate for virology, and electrocardiogram. Once hypocalcemia was established, a bone profile including ALP, PTH concentration, 25(OH)-D and 1, $25(OH)_2$-D was performed with a wrist radiograph.

Among infants who were diagnosed with vitamin D deficiency one infant required brief ventilatory support for uncontrolled apnea. Presenting symptoms, which were classified as frightening episodes by the care givers included apnea and cyanotic spells in 3 infants, marked limpness with cyanosis in one infant, and frequent choking and uncontrolled focal seizures in one infant. All the assembled cases were of Saudi Arabian ethnicity living in urban areas. Maternal characteristics included a sedentary lifestyle, lack of sun exposure, poor vitamin, and calcium supplements during pregnancy and lactation, and 4 infants were exclusively breast fed; and one partially breast fed. Similarly, none of the infants had received vitamin D supplements, or sun exposure.

Table 1 summarizes the biochemical profiles of each infant at the time of diagnosis. All infants were hypocalcemic with normal ALP and normal PO_4. Normal ALP levels have been previously documented with acute presentations of vitamin D deficiency in association with both hypo and normocalcemia and it is proposed to be due to the high metabolic demands occurring during the period of active growth, which

Table 1 - Summary of the biochemical profiles of 5 infants at the time of diagnosis.

Patients	Ca^{++} (mg/dl)	PO_4 (mg/dl)	25(OH)-D (ng/ml)	$1,25(OH)_2$-D (pmol/ml)	PTH (pg/ml)	Alkaline phosphatase (U/L)
Patient1	6.2	8.5	4	Not carried out	Not carried out	194
Patient 2	4.4	7.6	6	288	338	789
Patient 3	5.9	6.1	10	Not carried out	137.4	651
Patient 4	5.8	6.6	7	84	351	420
Patient 5	4.8	8.6	8	236	347	273
Reference range	8.7-10 mg/dl	4-9 mg/dl	>20 ng/ml	25-45 pg/ml	8-51 pg/mL	<600 IU/L

Ca^{++} - serum calcium, PO_4 - serum phosphorus, 25(OH)-D - 25-hydroxyvitamin D, 1, $25(OH)_2$-D - 1, 25-dihydroxyvitamin D, PTH - parathyroid hormone, U/L - units per liter, IU/L - international units per liter, pg\ml - picograms per milliliter, pmol/ml - picomoles per liter, ng/ml - nanograms per milliliter, mg/dl - milligrams per deciliter

precede the onset of radiological rickets.[2] All infants in our report had low serum levels of 25(OH)-D while PTH levels were consistently elevated. No skeletal or radiological deformities were found, and brain CT scans, and electroencephalography were all normal.

Despite the advantage of sunlight as a natural source of vitamin D in the Kingdom of Saudi Arabia, vitamin D deficiency remains a major health burden.[3] This is because many cultural and social norms including: traditional skin-covered dress wear, closed transportation system services, indoor activities, and sedentary life patterns collectively result in minimal, if any, exposure of the body to sunlight.[3] Vitamin D deficiency may present early in life, especially in an infant born to a vitamin D deficient mother who is exclusively breast fed. Symptoms such as apnea, convulsions, and stridor during the hypocalcemic phase of nutritional rickets, constitute the early phase and most serious stage of vitamin D deficiency.[2] Ladhani et al[2] described 17/29 (57%) children who had hypocalcemic symptoms without radiological findings, and 82% were less than 6 months of age. All our cases had maternal risk factors for congenital vitamin D deficiency, which resulted in life threatening presentations in infancy that significantly increased direct hospital costs due to unexpected PICU admission and prolonged hospital stay. These adverse events are preventable if "at risk" mothers' are identified early in pregnancy, properly counseled on potential environmental and demographic risk factors, and both mother and infant are given adequate vitamin D supplementation.[1]

An ALTE is common during infancy. It represents approximately 0.6-0.8% of all hospital emergency visits less than one year of age often posing as a diagnostic and treatment challenge as full cardio respiratory resuscitation may be necessary. Although our study was not designed as a case-control investigation the possibility that both ALTE and Vitamin D deficiency are inter-related pathophysiologically is likely, with hypocalcemia being the precipitating etiology for the episode of ALTE. Hypocalcemia has been well described in the literature, as a primary cause for ALTE.[4] Few reports however have concurrently reported on low plasma 25(OH)-D levels that have conclusively defined vitamin D deficiency as a cause of ALTE.[5] Maiya et al[5] described 16 infants with vitamin D deficiency as a cause of life-threatening heart failure due to severe cardiomyopathy that required intensive circulatory support. Six patients had a cardiac arrest and 3 died. Limitations include the descriptive nature of our study, small sample size confined to a single institution, which limits generalizability of the results and the absence of controls to statistically validate the proposed association of ALTE with vitamin D deficiency.

Vitamin D replacement therapy was started once the diagnosis of Vitamin D deficiency was confirmed. All infants received alphacalcidol in conjunction with intravenous calcium to control the profound hypocalcemia. This was titrated according to the Ca^{++} and 25(OH)-D response. Oral calcium supplements were stopped 3-6 weeks later, and all infants were eventually stabilized on a daily, oral dose of 400 IU of vitamin D3 (cholecalciferol). All mothers were screened and found to have severe vitamin D deficiency and were referred to an endocrinologist and nutritionist for proper counseling and follow-up and were started on vitamin D and calcium supplements.

We therefore recommend that 25(OH)-D should be considered part of the secondary biochemical assessment in any infants' with ALTE who are found to have hypocalcemia, especially dark-skinned children or those who reside in countries where exposure to sun light is limited due to geographical or traditional factors. Serum 25(OH)-D <20 ng/ml (50 nmol/l) confirms the diagnosis and is the most sensitive and earliest parameter of vitamin D deficiency.[1] Other diagnostic investigations should include: serum PO4, PTH, ALP levels, and a skeletal survey to exclude radiological

changes associated with vitamin D deficiency. All of our cases had hypocalcemia, hyperphosphatemia, and raised PTH levels with normal radiographs. Early recognition of the problem will avoid improper use of anti-epileptic drugs to control seizures, relieve parent and clinician anxiety, and decrease hospital costs and national healthcare expenditure.

In summary, despite the availability of cheap and effective methods of prevention, vitamin D deficiency continues to be a major public health problem in the Kingdom of Saudi Arabia and worldwide. It may present with ALTE without physical findings, or radiological changes of rickets. During early infancy, it could result in serious sequelae with prolonged hospitalization in intensive care. Once confirmed the treatment protocol involves correction of hypocalcemia and normalizing vitamin D stores. Treatment response and close on-going surveillance of the infant should be executed by the primary care pediatrician. In addition, the mother requires full nutritional assessment and counseling with regard to daily vitamin D intake and supplementation. Every infant who is partially or exclusively breastfed should receive a minimum of 400 IU/day of vitamin D3 commencing soon after birth until fortified foods that meet the minimal daily requirement of vitamin D are introduced. Supportive, maternal-child, public health policies are warranted to improve vitamin D intake for pregnant and lactating women. Preventive measures including community wide education on risk factors associated with vitamin D deficiency should be instituted to reduce the burden of this increasingly common illness.

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