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Case Report

A case report on anti-epileptic drugs associated cerebral palsy and rickets

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ABSTRACT

Seizures are incredibly widespread all around the world, today. A seizure is often described as a transient alteration in the electrical activity of the brain. This required the treatment with antiepileptic drugs (AEDs). The majority of AEDs lower vitamin D levels. Vitamin D is found to be crucial for intestinal absorption of calcium, magnesium, and phosphate which helps to build and mineralize bones. Vitamin D deficiency has been seen to be a causative reason for cerebral palsy which is a neurological illness that affects movement and muscle coordination, permanently. It has been observed to manifest in infancy or early childhood due to vitamin D deficiency due to long term use of AEDs making it severe due to malnourishment. This case reports the use of antiepileptic drugs leading to cerebral palsy due to vitamin D deficiency. Therefore, by this case report we want to alert the readers and healthcare professionals about the possible adverse effects of AEDs and to be aware of them.

Keywords: AEDs, Vitamin D, Cerebral palsy, Rickets, Seizures

INTRODUCTION

The most prevalent neurological condition affecting children nowadays is seizure. In the first 16 years of life, 4-10% of children have been observed to have at least one seizure attack. A seizure is a brief episode of aberrant brain electrical activity that alters movement or behavior for which antiepileptic drugs (AEDs) is use.[1] The antiepileptic drugs are classified as enzyme-inducing (primidone, oxcarbazepine, topiramate, phenytoin, carbamazepine, phenobarbital), non-enzyme-inducing (sodium valproate, levetiracetam, gabapentin, ethosuximide, vigabatrin, zonisamide, pregabalin, and tiagabine).[2] The use of AEDs is said to result in vitamin D malabsorption or deficiency by a certain mechanism involving cytochrome enzyme. 90% of vitamin D required for the body is synthesized in the skin. After being exposed to sunlight, 7-dehyrocholesterol is converted to vitamin D3 (cholecalciferol) in the skin. Vitamin D is converted to 25-OHD (calcifediol) in the liver with the help of 25-α-hydroxylase and then to 1, 25-dihydroxy D_3 (calcitriol) by the action of 1α hydroxylase in the kidney. Through the action of the enzyme cytochrome P24, vitamin D3 is broken down in the kidneys to produce the metabolites 24, 25 dihydroxy-vitamin D3 and 1α, 24, 25 trihydroxy-vitamin D3. Studies conducted in vitro show that cytochrome P450 3A4 converts 1, 25-dihydroxy vitamin D3 into inactive metabolites in the liver and small intestine, where it is virtually non-existent. This causes a reduction in intestinal calcium absorption. Notably, cytochrome P450-3A4 catalyzes the hydroxylation of 25-hydroxy vitamin D3 into 25-dihydroxy vitamin D3. Antiepileptic medications increase the activity of hepatic cytochrome P450 enzymes, particularly cytochrome P450 3A4, which increases vitamin D catabolism and decreases calcium absorption from the gut, causing hyperparathyroidism and increased calcium demineralization from the bones.[3] Numerous investigations have discovered that AED use contributes to poor vitamin D status and cerebral palsy (CP) as

frequent co-morbid illnesses.[4,5] The neurological condition known as cerebral palsy (CP) is seen to first appear in childhood and disrupts the development of the muscles that control movement and posture.[6] Further, daily activities are restricted for kids with cerebral palsy such as mobility, feeding, dressing, bathing, and other involuntary movements are all impacted by altered muscle tone, unsteady gait, balance problems, and impaired social functioning. Typical nutritional deficiencies in these people include a lack of calcium consumption and a deficiency in 25-hydroxyvitamin D.[7] As a result of altered vitamin D, calcium, and phosphorus metabolism, rickets is now a common condition seen in patients with long term AED usage.[8] Lower limb abnormalities, delayed growth, muscle weakness, thickened wrists and ankle and delayed motor skill are some of the clinical signs of rickets. Children aged 6 to 24 months are at greater risk of developing rickets due to rapid bone growth during this time and other risk factors include insufficient sunlight exposure, dark skin, decreased intake of vitamin D.[9,10] In this case report, we elaborate the long term use of antiepileptic drugs which has led to the occurrence of cerebral palsy and rickets in a child.

CASE REPORT

We present a case of 14 years' male pediatric patient who was admitted to Gandhi Hospital, Telangana with chief complaints of vomiting, loose motions and fever for two days. According to his current medical history**,** the fever was mild, intermittent and not accompanied by chills or rigors. Patient could hold his neck and sit with support but cannot stand or walk. From the age of 7 years, he suffered episodes of seizures and was on anti-epileptic drugs such as sodium valproate and clobazam. It was observed that he had developed cerebral palsy followed by a mental disability later on. On examination the following data was noted: Patient was conscious, coherent, and afebrile. His blood pressure was 120/80 mm Hg. CVS –s_1s_2+, respiratory system- BAE+, P/A- soft. Height was 119 cm. Weight was 14 kg. Body mass index (BMI) was 10.78 kg/m^2. Head circumference was 42 cm. The head-to-toe examination revealed that appearance was normal. Eye examination showed no bitot's spots. Lips - no angular cheilitis. Nails were not brittle and no clubbing. The skin was normal and healthy. No enlargement of the thyroid gland. The child was depicted with knee, short stature, pectus carinatum, rachitic rosary, Harrison's sulcus, pigeon chest and widening of the bilateral joint of lower limbs. The clinical features presented are shown in (Figures 1 and 2).

The clinical laboratory test revealed that hemoglobin level was as low as 9.6 gm/dl and calcium level was 7.7 mg/dl. According to all the subjective and objective data, the physician confirmed that the use of long-term antiepileptic drugs was associated with cerebral palsy and rickets. However, the patient was admitted for acute gastroenteritis treatment. The medications were prescribed for 14 days from the day of admission as shown in (Table 1).

Table 1: Medications prescribed.

Medications prescribed	Doses	Route of administration	Duration
Inj ciprofloxacin	200 mg	IV	bid
Inj metronidazole	0.5 gm	IV	tid
Inj pantoprazole	40 mg	IV	bid
Inj ondansetron	4 mg	IV	bid
T. lactic acid bacillus	120 million spores	PO	tid
Syp. sodium valproate	200 mg	PO	bid
T. clobazam	5 mg	PO	H/S
T. Ca^{2+} + D_3	500 mg	PO	OD

Figure 1: General appearance of child.

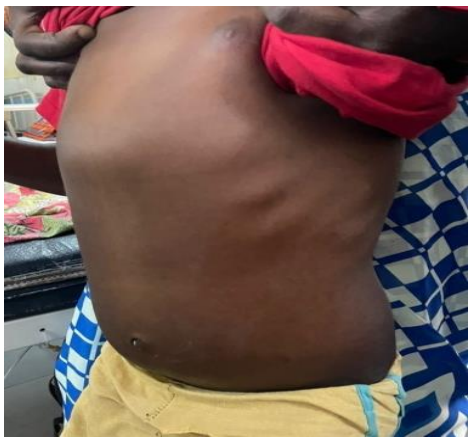

Figure 2: Pigeon chest.

Following the medication therapy, the patient recovered from acute gastroenteritis and was sent home after 14 days. A protein-rich diet was advised. The discharge medications prescribed were: syrup sodium valproate 5 ml BID, T. clobazam 5 mg H/S, vitamin B12 OD and ongoing calcium and vitamin D3 supplements were recommended by the physician.

DISCUSSION

This is a case of a 14 years old child who had suffered seizures when he was 7 years old. Later, he developed cerebral palsy and a mental disability and was underweight due to retardation of growth and improper diet. He had been on clobazam and sodium valproate the two antiepileptic drugs from 7 years of age. It was observed from previous literature that with long-term use of sodium valproate, individuals had acquired cerebral palsy and vitamin D deficiency. Cerebral palsy was the most frequent motor disability in childhood and associated with a high incidence of seizure disorder. Evidence from a meta-analysis showed that children receiving long-term valproate therapy had lower levels of vitamin D.[11] An Indian case-control study reported 61% vitamin D insufficiency and 32% deficiency in children with CP.[12] Our patient's clinical tests showed low vitamin D levels which caused muscle soreness, parenthesis, decreased muscle strength, and balance issues. This was mostly due to AED's long-term use for seizures. Hence, our findings can be co-related with that of past literature studies. The intestinal absorption of calcium, magnesium, and phosphate which facilitates bone mineralization and growth is significantly aided by vitamin D. For children to be in good health, 600 IU of vitamin D per day is advised. On the other hand, according to specialists in bone health, children with CP require greater dosages of 800-1000 IU/day to meet their vitamin D needs.[10] For the prevention of rickets good balanced diet which is rich in calcium and sufficient sun exposure are mainly necessary. Therefore, it is proposed that vitamin D levels be tested at regular intervals when the patient is taking AEDs and has cerebral palsy.

CONCLUSION

Clinicians should always monitor the vitamin D level, calcium levels, and overall well-being when a patient is on antiepileptic medications. A proper nutrition and calcium diet should be advised if the child is receiving antiepileptic medications. Awareness programs must be implemented to educate the rural population on disease, medication usage, and possible adverse effects. Moreover, from this case we wanted to draw the attention of healthcare professionals to possible complications associated with AED's long-term use.

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