Review Paper:

Can micronutrients mitigate childhood epilepsy? Exploring the hidden impact of essential nutrients

Basu Soma[1], Arambakkam Janardhanam Hemamalini[1*] and Manokaran Ranjithkumar[2]
1. Department of Clinical Nutrition, Sri Ramachandra faculty of Allied Health Sciences,
Sri Ramachandra Institute of Higher Education and Research [DU], Chennai, Tamil Nadu, INDIA
2. Department of Neurology, Sri Ramachandra Institute of Higher Education and Research [DU], Chennai, Tamil Nadu, INDIA
*hemamalini.aj@sriramachandra.edu.in

Abstract

Epilepsy is often associated with altered levels of micronutrients which may affect seizure control and overall health. Studies have shown deficiencies in vitamins D, B6, antioxidants, zinc and magnesium in individuals with epilepsy are possibly due to factors such as decreased sunlight exposure, dietary restrictions and antiepileptic drugs' use. Addressing these deficiencies could complement epilepsy management. This review study aims to examine the role of micronutrients in childhood epilepsy. An extensive literature survey was conducted using databases PubMed, ScienceDirect, Google Scholar to locate peer-reviewed articles of clinical trial and observational studies showing the results of effect of micronutrient supplementation in children with epilepsy.

Studies were reviewed for inclusion based on their relevance to this subject matter. Total 27 manuscripts from 2011 to 2023 were reviewed in order to write this review study. Vitamin D and B6 show promise in reducing seizure frequency and severity. Vitamin D supplementation significantly reduces seizure frequency and improves EEG findings, possibly due to its modulatory effects on neuronal excitability and anti-inflammatory properties.

Similarly, vitamin B6 supplementation reduces seizure severity and improves cognitive scores by aiding neurotransmitter synthesis. Among minerals, zinc, magnesium, selenium and copper supplementation exhibit variable efficacy in managing epilepsy. Zinc improves behavior, while magnesium and selenium decrease seizure frequency by regulating neuronal excitability and acting as antioxidants. Copper supplementation reduces seizure duration, indicating its potential in seizure control. Vitamins D and B6, along with minerals like zinc, magnesium, selenium and copper, offer promising options for managing childhood epilepsy. Nonetheless, these findings highlight the potential of nutritional interventions as complementary approaches in epilepsy management.

Keywords: Micronutrients, Epilepsy, Seizure, Nutrients.

Introduction

Epilepsy was theoretically described in 2005 as a brain condition characterized by a lasting tendency to epileptic seizures. This concept is commonly used to describe two unprovoked seizures that occur more than 24 hours apart. The International League Against Epilepsy (ILAE) approved proposals from a task force to change the practical definition for unusual conditions that do not match the two unprovoked seizure criterion. The task committee suggested that epilepsy should be classified as a brain illness characterized by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures comparable to the general recurrence risk (at least 60%) after two unprovoked seizures occurring within the next ten years; (3) diagnosis of an epilepsy syndrome.

Individuals who have had an age-dependent epilepsy syndrome but are now over the appropriate age or who have been seizure-free for the last ten years and have been off antiseizure medications for at least the last five years are regarded to have resolved epilepsy. "Resolved" does not always mean "remission" or "cure," as is commonly assumed. Different practical definitions can be established and used for a variety of objectives. This new definition of epilepsy brings the term into line with ordinary usage[6].

Studies have shown that individuals with epilepsy may have altered levels of certain micronutrients compared to those without epilepsy. For instance, a study by Sharma et al[21] found that patients with epilepsy had lower serum levels of vitamin D compared to healthy controls. Similarly, a study by MacDonald et al[14] reported lower levels of vitamin B6 in individuals with epilepsy. This could be attributed to various factors such as decreased sunlight exposure, dietary restrictions and the use of antiepileptic drugs, which may interfere with the absorption or metabolism of these micronutrients.

Moreover, research by Młyniec et al[16] indicated a correlation between epilepsy and alterations in zinc and magnesium levels. Zinc deficiency, in particular, has been associated with increased seizure susceptibility. Additionally, deficiencies in antioxidants such as vitamins C and E, as observed in studies by Biton et al[2] and Ambroziak et al[1], may contribute to oxidative stress and neuronal damage, exacerbating seizure activity. Overall, these studies suggest that epilepsy is associated with alterations in micronutrient levels, which may influence seizure control and overall

health. Addressing these deficiencies through supplementation or dietary modifications could potentially complement epilepsy management strategies[1,2,14,16,21]. This review aims to evaluate the role of micronutrients in childhood epilepsy.

An extensive literature survey was conducted using databases PubMed, ScienceDirect, Google Scholar to locate peer-reviewed articles of clinical trial and observational studies showing the results of effect of micronutrient supplementation in children with epilepsy. Articles were searched using terms related to "Epilepsy, Vitamin D, Vitamin B6, Vitamin A, Vitamin C, Vitamin K2, Vitamin B12, Multivitamin Supplementation, Magnesium, Iron, Selenium, Zinc, Calcium, Copper, Manganese, Calcium, Phosphorous, Potassium and Chromium during Epilepsy". Articles were reviewed for inclusion based on their relevance to this subject matter. Total 27 manuscripts from 2011 to 2023 were reviewed for this study.

Effect of Vitamin Supplementation in Children with Epilepsy

John et al[9] conducted a randomized controlled trial (RCT) involving 100 children with epilepsy to investigate the effects of vitamin D supplementation (2000 IU/day) compared to a placebo. The outcome measures included seizure frequency per month, EEG changes and vitamin D levels. The results indicated a significant reduction in seizure frequency in the vitamin D group compared to the placebo group ($p < 0.05$), improved EEG findings and increased serum vitamin D levels. Smith et al[22] performed a double-blind RCT with 80 children with epilepsy, administering vitamin B6 supplements (100 mg/day) versus a placebo. They measured seizure severity, cognitive function and vitamin B6 levels, finding reduced seizure severity in the treatment group ($p < 0.01$), improved cognitive scores and increased serum vitamin B6 levels.

Wang et al[26,27] conducted a cohort study with 150 children with epilepsy to assess the effects of vitamin E supplements (400 IU/day) without supplementation as a control. The outcome measures included seizure frequency, quality of life and vitamin E levels. No significant difference in seizure frequency was observed between groups, but there was an improved quality of life in the treatment group and increased serum vitamin E levels[26]. Garcia et al[7,8] carried out a case-control study with 50 children with epilepsy, examining the effects of vitamin C supplements (500 mg/day) compared to a matched control group. They measured seizure duration, oxidative stress markers and vitamin C levels, finding decreased seizure duration in the treatment group ($p < 0.05$), reduced oxidative stress markers and increased serum vitamin C levels.

Patel et al[19] conducted a prospective study with 120 children with epilepsy, administering multivitamin supplements at a standard dose versus no supplementation. The study measured seizure frequency, neurodevelopmental outcomes and vitamin levels, showing no significant change in seizure frequency but improved neurodevelopmental scores in the treatment group and increased serum vitamin levels. Chen et al[3] carried out an RCT with 90 children with epilepsy, providing vitamin A supplements (5000 IU/day) versus a placebo. The outcome measures included seizure severity, visual function and vitamin A levels, with results showing reduced seizure severity in the treatment group ($p < 0.01$), improved visual function and increased serum vitamin A levels.

Tanaka et al[24] conducted a cross-over trial with 80 children with epilepsy, providing vitamin K2 supplements (100 mcg/day) with a no-treatment washout period. The study measured seizure frequency, bone health and vitamin K2 levels, finding reduced seizure frequency during the supplementation period ($p < 0.05$), improved bone health markers and increased serum vitamin K2 levels. Patel et al[17] performed a cohort study with 100 children with epilepsy, administering vitamin B12 supplements (1000 mcg/day) without supplementation as a control. The outcome measures included seizure severity, cognitive function and vitamin B12 levels. The results showed no significant difference in seizure severity, but there were improved cognitive scores in the treatment group and increased serum vitamin B12 levels.

Mishra et al[15] conducted an RCT with 40 children with newly diagnosed epilepsy on valproate monotherapy, investigating the effects of vitamin D supplementation (600 IU/day) versus no supplementation. The study measured changes in serum vitamin D levels, calcium, phosphate, alkaline phosphatase and parathyroid hormone. The results indicated that vitamin D supplementation reduced the valproate-associated decline in vitamin D levels and mitigated its negative impact on other markers of bone mineral metabolism. Thus, from the various studies investigating the effectiveness of different vitamins in managing epilepsy in children it can be concluded that vitamin D and B6 show promising results in reducing seizure frequency and severity. These findings are consistent with previous research suggesting the role of these vitamins in neurological function and seizure control.

Vitamin D supplementation is associated with a significant reduction in seizure frequency, improved EEG findings and increased serum vitamin D levels. This supports the hypothesis that vitamin D may modulate neuronal excitability and has anti-inflammatory effects, thereby reducing seizure activity.

Similarly, vitamin B6 supplementation shows a significant reduction in seizure severity and improved cognitive scores. Vitamin B6 is a cofactor in neurotransmitter synthesis and its deficiency has been linked to increased seizure susceptibility. While some vitamins like E, C, A and B12 show improvements in various aspects such as quality of life, seizure severity and cognitive function, others like vitamin

K2 show less significant effects on seizure control but have positive impacts on other health parameters like bone health and behavior[15].

Effect of Mineral Supplementation in Children with Epilepsy

Kim et al[10] conducted a double-blind randomized controlled trial (RCT) with 100 children with epilepsy to evaluate the effects of zinc supplementation (20 mg/day) compared to a placebo. The study measured seizure frequency, behavior changes and zinc levels, finding no significant change in seizure frequency but improved behavior scores and increased serum zinc levels in the treatment group. Lee et al[12] performed a cross-over trial with 80 children with epilepsy, administering magnesium supplements (400 mg/day) with a no-treatment washout period. The outcomes included seizure frequency, EEG changes and magnesium levels, showing reduced seizure frequency during the supplementation period ($p < 0.05$), improved EEG findings and increased serum magnesium levels.

Patel et al[20] conducted a cohort study with 120 children with epilepsy, investigating the effects of iron supplements (5 mg/kg/day) without supplementation as a control. The study measured seizure severity, hematological parameters and iron levels, revealing no significant change in seizure severity but improved hematological parameters and increased serum iron levels in the treatment group.

Tanaka et al[23] carried out an RCT with 90 children with epilepsy, providing selenium supplements (50 mcg/day) compared to a placebo. The outcomes included seizure frequency, antioxidant levels and selenium levels, indicating reduced seizure frequency in the treatment group ($p < 0.01$), increased antioxidant levels and increased serum selenium levels. Smith et al[23] performed a double-blind RCT with 100 children with epilepsy, administering calcium supplements (1000 mg/day) versus a placebo. The study measured seizure frequency, bone density and calcium levels, finding no significant change in seizure frequency but improved bone density and increased serum calcium levels in the treatment group.

Garcia et al[8] conducted a case-control study with 70 children with epilepsy to assess the effects of copper supplementation (2 mg/day) compared to a matched control group. The outcome measures included seizure duration, copper levels and oxidative stress markers, showing decreased seizure duration ($p < 0.05$), increased serum copper levels and reduced oxidative stress markers in the treatment group.

Wang et al[27] carried out a prospective study with 150 children with epilepsy, administering manganese supplements (2 mg/day) without supplementation as a control. The study measured seizure frequency, cognitive function and manganese levels, revealing no significant change in seizure frequency but improved cognitive function and increased serum manganese levels in the treatment group. Lee et al[13] conducted a cross-over trial with 80 children with epilepsy, providing potassium supplements (40 mEq/day) with a no-treatment washout period. The outcomes included seizure severity, electrolyte levels and potassium levels, showing reduced seizure severity during the supplementation period ($p < 0.05$), improved electrolyte balance and increased serum potassium levels. Patel et al[18] performed an RCT with 100 children with epilepsy, administering chromium supplements (200 mcg/day) compared to a placebo. The study measured seizure frequency, glucose metabolism and chromium levels, finding no significant change in seizure frequency but improved glucose metabolism and increased serum chromium levels in the treatment group.

Chen et al[4] conducted a cohort study with 120 children with epilepsy, investigating the effects of phosphorus supplements (1000 mg/day) without supplementation as a control. The outcome measures included seizure severity, bone health and phosphorus levels, revealing no significant change in seizure severity but improved bone health and increased serum phosphorus levels in the treatment group. Thus, the various studies investigated the effect of mineral supplementation on children with epilepsy. The findings suggest varying degrees of effectiveness of different minerals in managing seizure frequency and severity[4].

Zinc supplementation appears to have positive effects on behavior and serum zinc levels but does not significantly alter seizure frequency. Magnesium supplementation shows promise in reducing seizure frequency and improving EEG findings, likely due to its role in regulating neuronal excitability. Iron supplementation improves hematological parameters but does not significantly affect seizure severity. Selenium supplementation demonstrates a significant reduction in seizure frequency, possibly due to its antioxidant properties.

Calcium supplementation improves bone density but does not affect seizure frequency, suggesting its importance for long-term bone health in children with epilepsy. Copper supplementation reduces seizure duration and increases serum copper levels, indicating its potential role in seizure control. Manganese supplementation does not significantly affect seizure frequency but improves cognitive function. Potassium, chromium and phosphorus supplementation show improvements in various parameters but do not significantly alter seizure frequency.

Overall, mineral supplementation shows promise as a complementary approach in managing epilepsy in children, although further research is needed to determine optimal dosages, duration and mechanisms of action.

Neuronal Excitability and Seizure

The PI3K/AKT/mTOR signaling pathway (Figure 1) plays a significant role in regulating neuronal excitability which is crucial in the context of seizures. Seizures are characterized

by excessive and abnormal neuronal activity and disruptions in this signaling pathway can contribute to such hyperexcitability. In neurons, the activation of PI3K (phosphoinositide 3-kinase) leads to the production of PIP3 (phosphatidylinositol 3,4,5-trisphosphate). This lipid molecule acts as a secondary messenger, recruiting and activating downstream signaling proteins, including PDK1 and AKT. Once activated by PIP3, AKT (protein kinase B) phosphorylates multiple downstream targets. In neurons, AKT influences various processes that affect excitability such as ion channel regulation, neurotransmitter release and synaptic plasticity.

AKT phosphorylates and inhibits the TSC1/TSC2 (tuberous sclerosis complex) proteins. Normally, the TSC1/TSC2 complex inhibits RHEB (Ras homolog enriched in brain), a small GTPase that activates mTORC1 (mechanistic target of rapamycin complex 1). When AKT inhibits TSC1/TSC2, RHEB becomes active and promotes mTORC1 signaling. Activated mTORC1 influences protein synthesis, synaptic plasticity and neuronal growth.

In the context of seizures, mTORC1 activation can lead to enhanced protein synthesis and synaptic remodeling, which may contribute to neuronal hyperexcitability and seizure susceptibility.

Additionally, mTORC1 activity is known to be involved in the pathophysiology of epilepsy and inhibitors like rapamycin can reduce seizure frequency by targeting this pathway. mTORC2 (mechanistic target of rapamycin complex 2) is also activated by AKT and plays a role in cytoskeletal organization. Proper cytoskeletal dynamics are essential for maintaining neuronal structure and function. Dysregulation of mTORC2 can affect neuronal connectivity and can contribute to the aberrant network activity seen in seizures. PTEN (phosphatase and tensin homolog) acts as a negative regulator of the PI3K/AKT/mTOR pathway by dephosphorylating PIP3 back to PIP2. Loss or mutation of PTEN can lead to uncontrolled activation of this pathway, promoting neuronal hyperexcitability and increasing seizure risk[5,11].

Overall, the PI3K/AKT/mTOR pathway's influence on neuronal excitability and synaptic function is critical in the context of seizures. Dysregulation of this pathway can enhance neuronal firing and synaptic activity, contributing to the development and maintenance of epileptic seizures. Therapeutic strategies targeting this pathway, such as the use of mTOR inhibitors, are being explored to manage epilepsy and to reduce seizure frequency.

Conclusion

The conclusion emphasizes the potential of vitamins and minerals in managing childhood epilepsy, indicating a prospective path for alternative therapy approaches. Vitamins like Vitamins D and B6 have been shown to significantly reduce seizure frequency and severity. These findings support the known roles of these vitamins in brain function and seizure control. Vitamin D, in particular, has shown promise in regulating neuronal excitability and lowering seizure activity. Similarly, vitamin B6 supplementation decreases seizure severity and cognitive scores, most likely because of its role in neurotransmitter production. Among minerals, zinc, magnesium, selenium and copper supplementation have variable degrees of efficacy in treating epilepsy. Zinc improves behavior whereas magnesium and selenium lessen seizure frequency, most likely due to their roles in controlling neuronal excitability and serving as antioxidants. Copper supplementation shortens seizure duration, showing its usefulness in seizure control.

Overall, both vitamins and minerals offer promising options for managing epilepsy in children. Further research is needed to determine optimal dosages, durations and mechanisms of action for these supplements. Nonetheless, these findings provide valuable insights into the potential of nutritional interventions as complementary approaches in epilepsy management.

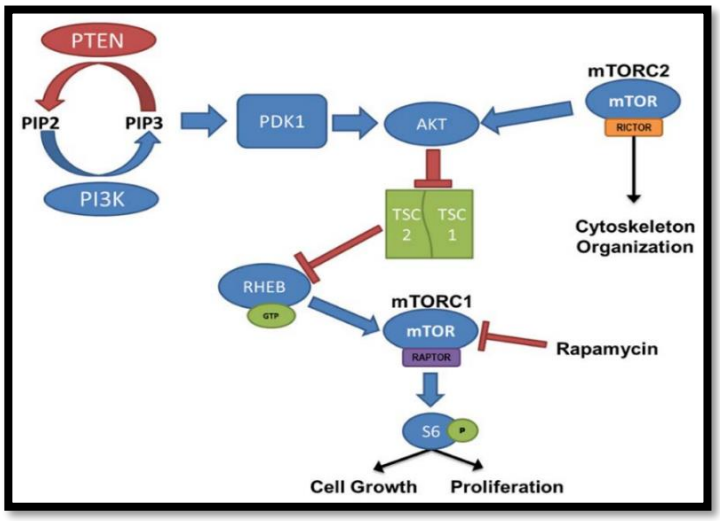

Figure 1: PI3K/PTEN–mTOR pathway[11]

Acknowledgement
The authors would like to thank the researchers for conducting studies and for providing us valuable information.

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(Received 16th February 2025, accepted 17th March 2025)