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FOLATE DEFICIENCY INDUCED BY ANTIEPILEPTICS: A CASE SERIES

Abna Salahudeen[1], Arppana Thomas[2], Aarsha Sadar[3], Arunraj C. N.[4]
[1]Intern, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India.
[2]PG Resident, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India.
[3]Assistant Professor, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India.
[4]Professor, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India.

Corresponding Author

Arunraj C.N.
Professor, Department of General Medicine, Travancore Medical College, Kollam, Kerala, India

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Abstract

Antiepileptic drugs are widely used for seizure management, but their long-term use has been associated with various side effects like osteoporosis, vitamin D deficiency, dysphagia, nephrotoxicity, depression and hepatotoxicity. It also causes hematological abnormalities which includes anemia, thrombocytopenia and folate deficiency. Folate plays a crucial role in neural function, DNA synthesis and erythropoiesis. Its depletion can lead to anemia, thrombocytopenia, and neurological complications. Long-term use of antiepileptics like sodium valproate, phenytoin, carbamazepine, and levetiracetam have been implicated in affecting folate metabolism through mechanisms such as enzyme induction, increased folate breakdown, impaired absorption, and competitive inhibition at folate receptor sites. This case series highlights the incidence of folate deficiency, anemia and thrombocytopenia in patients on treatment with anti-epileptics. Thus, awareness regarding antiepileptic-induced folate deficiency and monitoring hematological parameters, particularly folate level in patients taking antiepileptics can be helpful in early detection and prevention of complications. Intervention through folate supplementation can improve patient outcome and quality of life.

Keywords: Antiepileptics, folate deficiency, anemia, thrombocytopenia

INTRODUCTION

Epilepsy is a common neurological disorder requiring long-term antiepileptic therapy. But, the potential adverse effects on hematological parameters, particularly folate metabolism is rarely addressed.[1] Folate plays a crucial role in DNA synthesis, erythropoiesis, and neurological function. Several antiepileptics, including sodium valproate, phenytoin, carbamazepine, and levetiracetam,[2] have been associated with interference of folate metabolism, leading to its deficiency that may result in anemia, thrombocytopenia, and neurological complications. [2,3] The mechanisms include enzyme induction, increased folate catabolism, impaired intestinal absorption, and competitive inhibition at folate receptor sites. Identifying folate deficiency and initiating supplementation can prevent the risk of complications and improve patient outcome. Monitoring of serum folate levels in patients on chronic antiepileptic therapy can prevent delay in diagnosis of folate deficiency and complications such as anemia, fatigue and thrombocytopenia.[4] This case series presents four patients on long-term antiepileptic treatment who developed haematological abnormalities including anemia and thrombocytopenia and was found to have folate deficiency.

Case 1

A 21-year-old male student, diagnosed with focal epilepsy secondary to bilateral gliosis and static encephalopathy was admitted with lower respiratory tract infection. He was on sodium valproate (500 mg/day) and oxcarbazepine (600 mg/day) for 10 years. Examination revealed pallor and neurological signs, including sensory ataxia and tingling sensations over the feet. Laboratory findings showed macrocytic anemia, thrombocytopenia, with serum folate level markedly reduced to 0.803ng/ml (normal: 3-17ng/ml). vitamin B12 level was normal at 464 pg/ml (normal: 187-883 pg/ml). Iron studies were within normal limits. Peripheral smear showed macrocytic picture and thrombocytopenia (Figure 1). Patient was started on folate supplementation. After 4 weeks, his symptoms subsided, anemia and folate level improved.

Case 2:

A 57-year-old male, known case of seizure disorder for 6 years presented with cough, breathlessness, and generalised tiredness for 4 days. He was on sodium valproate (500 mg/day) and levetiracetam (500 mg/day) for 6years. Examination revealed pallor and signs of peripheral neuropathy. Laboratory results showed macrocytic anemia and thrombocytopenia.

Serum folate levels were low normal 4.08 ng/ml, while vitamin B12 level was normal at 480 pg/ml. Serum ferritin was also within normal limits. Peripheral smear showed macrocytic blood picture and thrombocytopenia (Figure 2). As he was having anemia and signs of neuropathy, folate supplementation 5 mg once daily was added. Patient improved clinically, anemia was corrected and his folate level improved on follow up after 4 weeks.

Case 3:
A 69-year-old female with seizure disorder for 12 years was admitted with hypertensive encephalopathy. She was on phenytoin (100mg/day) and levetiracetam (500 mg/day) for 12 years. General examination revealed pallor and her blood pressure was 190/110 mmHg. Peripheral smear showed macrocytic anemia (Figure 3). Serum ferritin and vitamin B12 levels were normal. Her folate level was reduced to 3.4 ng/ml. She was started on folate supplementation 5mg once daily. After 4 weeks, patient was symptomatically better with improvement in folate level.

Case 4:
A 75-year-old male, known case of seizure disorder for 10 years on levetiracetam (500 mg/day) was admitted with reduced appetite and tiredness for 2 weeks. On examination, patient had pallor and signs of peripheral neuropathy. Routine blood investigations showed severe anemia with macrocytic blood picture. Serial monitoring of platelet counts showed persistently low platelet count (around $85x10^9$/L). Serum folate level was significantly reduced to 1.5 ng/ml, while vitamin B12 levels was within normal limits. Peripheral smear showed macrocytic blood picture with thrombocytopenia (Figure 4). Patient was started on folate supplementation. After 4 weeks, patient was clinically and symptomatically better.

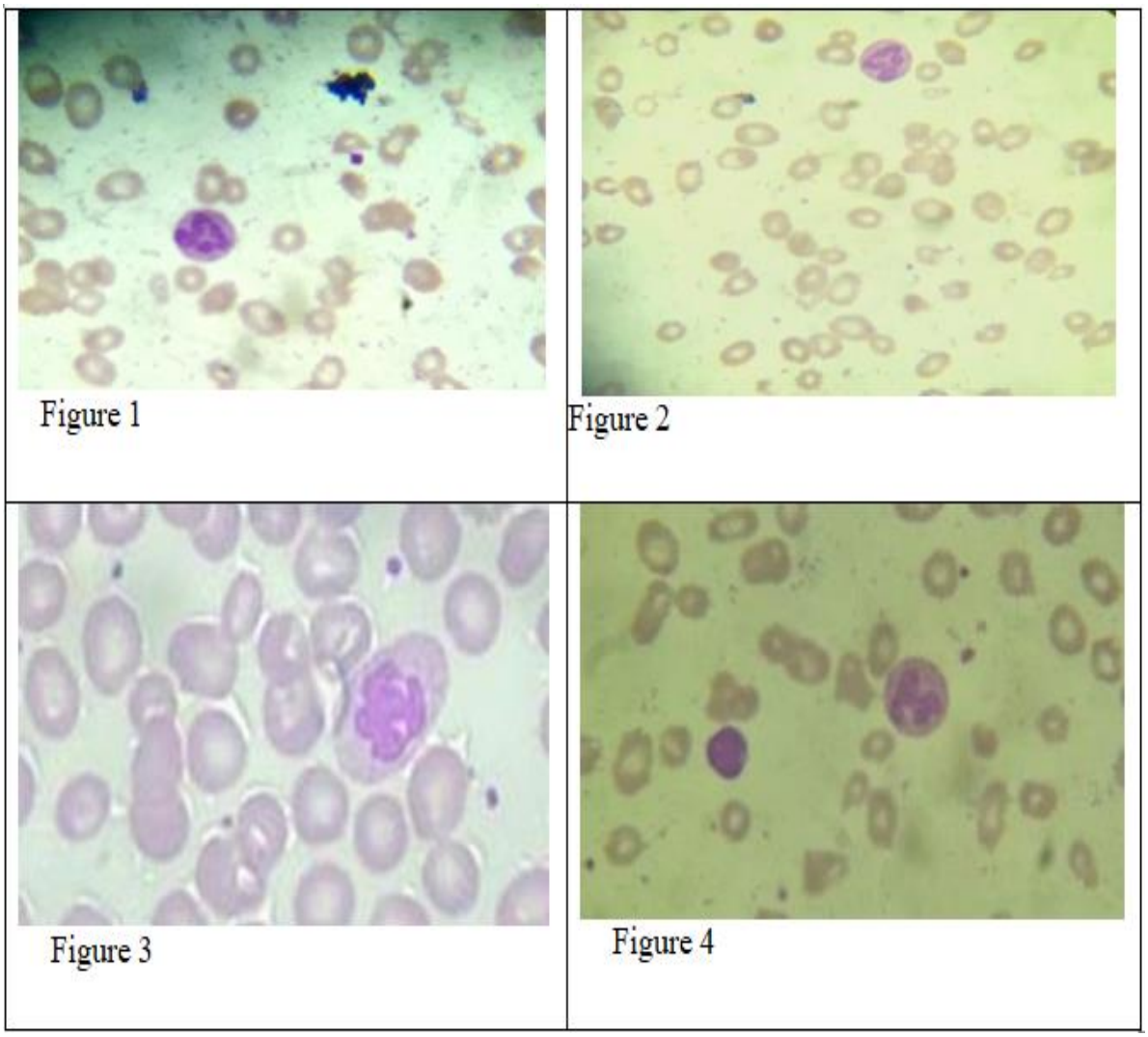

Figure 1,2,4: Peripheral smear showing macrocytic picture with hypersegmented neutrophil and thrombocytopenia.
Figure 3: Peripheral smear showing macrocytic blood picture with hypersegmented neutrophil.

Laboratory findings of the patients at the time of admission

PARAMETER	CASE 1	CASE 2	CASE 3	CASE 4	REFERENCE RANGE
Haemoglobin	11.3	9	11	8.9	12-18 gm/dl
Total count	8200	5000	8600	8800	4000-11000 cells/mm3
Red blood cells	3.94	3.2	3.65	3.1	4-5 millions/mm3
Mean Corpuscular Volume	95	102	97	99	82-92 fL
Mean Corpuscular Haemoglobin	28.7	28.1	30.1	28.7	27-32 pg/cell
Mean Corpuscular Haemoglobin Concentration	35	34	36	34	32-36 gm/dl
Platelet count	91	105	225	85	150- 450 x 10^9/L
ESR	5	16	10	10	0-20 mm/hr
CRP	62	6.4	1.6	1.6	<6 ng/L
Vitamin B12	464	480	1050	600	187-883 Pg/mL
Folic acid	0.803	4.08	3.4	1.5	3-17 ng/ml
Serum ferritin	80	150	90	100	Male (22-322 ng/dl) Female (10-291 ng/dl)

DISCUSSION

This case series highlights the potential hematological complications associated with long-term use of antiepileptic drugs, particularly sodium valproate, oxcarbazepine, phenytoin, and levetiracetam. These patients presented with various hematological abnormalities, including anemia, thrombocytopenia and folate deficiency. Other potential causes of anemia, such as infections, uncontrolled bleeding, systemic diseases, alcohol use, malignancy, malnutrition and use of other drugs interfering with folate metabolism were ruled out.

The first case was a young patient with focal epilepsy exhibited a pronounced macrocytic blood picture and persistent thrombocytopenia. The significant reduction in his serum folate levels aligns with the prolonged use of sodium valproate and oxcarbazepine, both of which are implicated in disrupting folate metabolism. Folic acid supplementation led to marked clinical improvement, underscoring the reversibility of antiepileptic-induced hematological changes with timely intervention.

In the second case, the middle-aged patient's peripheral neuropathy, anemia, and reduced folate levels highlight the cumulative effects of sodium valproate and levetiracetam over several years. Although folate levels were only mildly reduced, the symptoms improved with supplementation, suggesting that even borderline deficiencies can be clinically significant.

The third case illustrates how combined antiepileptic therapy, involving phenytoin and levetiracetam, can lead to folate deficiency with macrocytic anemia. This reinforces the need for routine monitoring of hematological parameters in patients receiving combination antiepileptic therapy.

In case 4, the elderly patient's severe anemia and thrombocytopenia reflect the potential of antiepileptics like levetiracetam to induce folate deficiency. Despite being on therapy for only a year, the dramatic drop in folate levels and associated hematological abnormalities highlight the need for vigilance even with shorter duration of therapy.

Antiepileptic drugs are known to interfere with folate metabolism through multiple mechanisms which include inducing hepatic enzymes, accelerating the breakdown of folate and reducing its bioavailability and impaired folate absorption in

the gastrointestinal tract. [5,6] Other mechanisms include competitive inhibition at folate receptor sites, and the production of folate receptor autoantibodies. This might be the reason for features of folate deficiency even with normal folate levels.[7] These disruptions in folate metabolism are concerning, as folate plays a critical role in DNA synthesis, cellular repair, and erythropoiesis.[8,9] The synthetic form, folic acid, is given as dihydrofolate (DHF) and is converted to tetrahydrofolate (THF) by the action of the dihydrofolate reductase enzyme, then converts to 5,10-methylene tetrahydrofolate (5,10-MTHF), which can diverge down towards DNA synthesis.[10,11] Several antiepileptics are known to cause hematological side effects, ranging from mild thrombocytopenia and neutropenia to more severe conditions like aplastic anemia.[11,12] It was found that patients receiving carbamazepine, oxcarbazepine, phenytoin and sodium valproate were associated with lower mean serum folate levels.[12,13,14] These findings highlight the need for further research to establish the long-term effects of antiepileptics on folate metabolism and to develop guidelines on routine supplementation of folic acid in patients on long term antiepileptic therapy. In all our patients we ruled out other causes of anemia and folate deficiency, through a detailed history, clinical examination and relevant investigations. Hence, the probable etiology considered more likely is the use of antiepileptics. The findings from this case series emphasize the importance of regular hematological assessments in patients on long- term anti epileptics. Monitoring serum folate and Vitamin B12 levels, alongside complete blood counts, can help in the early detection of deficiencies and prevent complications such as anemia, thrombocytopenia and peripheral neuropathy. Furthermore, considering routine folate supplementation, particularly in high-risk populations, including elderly patients, who are on antiepileptic therapy can be helpful.

CONCLUSION

Folate deficiency is a potential but under-recognized side effect of long-term antiepileptic therapy. Regular monitoring of serum folate levels and hematological parameters is crucial for patients on chronic antiepileptic drug therapy. Early detection and intervention can help to reduce the adverse effects of folate deficiency and improve patient outcome and quality of life. This case series highlights the need for further research and standardized guidelines to address antiepileptic-induced folate deficiency.

Limitations

The findings of this case series are limited by the retrospective nature and the small number of patients included. Further prospective studies with larger sample sizes are needed to confirm these observations and comprehend the mechanisms of antiepileptic-induced folate deficiency.

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REFERENCES

1. Kırar H, Turkkan E, Uzunhan TA, Kaçar A, Sazak S, Dikker O, Dağ H. Evaluation of the effects of antiepileptic drugs on complete blood count parameters. J Surg Med. 2020;4(12):1108-1111.
2. Mahdavi A, Naeini AA, Najafi M, Ghazvini M, Maracy M. Vitamin B12 and Folate Status in Patients with Epilepsy Under Levetiracetam Monotherapy. Int J Prev Med. 2019 Mar 5; 10:32.
3. Bisi-Onyemaechi AI, Chikani UN, Uwaezuoke NA, Aronu AE, Ojinnaka NC. Serum folate levels in children on long-term anti-seizure medication in a Nigerian tertiary center Implications for practice and public health. Sci Prog. 2021 Oct;104(4):3685.
4. Kathiravan M, Kavitha S, Shanthi R. To determine the effect of long-term antiepileptic drug on the serum folate and vitamin B12 among epileptic patients. Sci Rep. 2021 Feb 23;11(1):4393.
5. Linnebank M, Moskau S and Semmler A. Antiepileptic drugs interact with folate and vitamin B12 serum levels. Ann Neurol 2011; 69: 352–359.
6. Huang HL, Zhou H, Wang N, Yu CY. Effects of antiepileptic drugs on the serum Folate and Vitamin B12 in various epileptic patients. Biomed Rep. 2016;5(4):413-416.
7. Weston J, Greenhalgh J, Marson AG. Antiepileptic drugs as prophylaxis for post craniotomy seizures. Cochrane Database Syst Rev 2015;3(9):210-213.
8. K. E. Elizabeth, H. Gopakumar, Philip Zachariah, Roy George Jacob. Valproate induced thrombocytopenia complicating acute febrile illness. Ann Indian Acad Neurol 2006; 9:230232.
9. Michael Linnebank MD, Susanna Moskau MD, Alexander Semmler MD, Guido Widman MD, Birgit Stoffel-Wagner Prof, Michael Weller Prof, Christian E. Elger Prof. Antiepileptic drugs interact with Folate and Vitamin B12 serum levels. Annals of Neurology. 2011;69(2).
10. Li C, Su L, Lao M, Zhu S, Ding M. Anemia secondary to the use of sodium valproate for preventing

postoperative seizures in a 79-year-old man: A case report. Medicine (Baltimore). 2018 Dec;97(50): 13626.
11. Kumar V, Aggarwal A, Sharma S, et al. Effect of carbamazepine therapy on homocysteine, vitamin B12 and folic acid levels in children with epilepsy. Indian Pediatr 2013; 50: 469–472.
12. A Verrotti, R Pascarella, D Trotta, T Giuva, G Morgese, F Chiarelli,
13. Hyperhomocysteinemia in children treated with sodium valproate and carbamazepine, Epilepsy Research, 2000;41(3); 253-257.
14. Kaczorowska-Hac B, Matheisel A, Maciejka-Kapuscinska L, Wisniewski J, Alska A, Adamkiewicz-Drozynska E, Balcerska A, Reszczynska I. Anemia secondary to valproic acid therapy in a 13-year-old boy: a case report. J Med Case Rep. 2012 Aug 10; 6:239.
15. Zhang C, Deng X, Wen Y, He F, Yin F, Peng J. First case report of cerebral folate deficiency caused by a novel mutation of FOLR1 gene in a Chinese patient. BMC Med Genet. 2020 Nov 26;21(1):235