Journal of Preventive and Population Health
https://jpphealth.com/

CASE REPORT

A case report of carbonic anhydrase II deficiency and literature review

Anas Alamri[1]

Full list of author information is available at the end of the article.

ABSTRACT

Background: Epilepsy is a chronic neurological illness characterized by two unprovoked seizures occurring more than 24 hours apart or a single seizure with a significant chance of recurrence. Carbonic anhydrase is a crucial enzyme in physiological functions. Carbonic anhydrase II (CA II) deficiency is a rare autosomal recessive disorder caused by mutations in the CA II gene and is mainly characterized by osteopetrosis. Recent research highlights the complex relationship between CA II and epilepsy, where it is hypothesized that CA II deficiency disrupts pH regulation in the brain, causing changes in neuroendocrine function that could influence seizure threshold. This dual effect indicates CA II's critical role in maintaining normal brain function and its potential implications for seizure development in related genetic disorders.

Case Presentation: A 22-year-old female with a history of absent seizures presented to the Emergency Department after a fall resulting in bruises post-convulsion. Diagnosed with epilepsy at age 12, her seizures, lasting 2-3 minutes, involve staring without tonic-clonic activity. She experienced intellectual disability and chronic bone pain. During examination, she demonstrated confusion and had two absent seizures. Vital signs were stable, with some laboratory findings indicating hyponatremia and hypokalemia. Despite treatment with Trileptal and Keppra, seizures remained uncontrolled, leading to a diagnosis of CA II deficiency, causing osteopetrosis and basal ganglia calcification. The treatment plan included stopping Keppra and initiating Depakine while maintaining the Trileptal dosage. Gene testing confirmed CA II deficiency.

Conclusion: This case is a rare case of epilepsy associated with CA II deficiency, a rare genetic disorder, with novel co occurrence of osteopetrosis. It emphasizes the importance of considering CA II deficiency in patients with unexplained bone and brain abnormalities and recommends genetic testing to confirm the diagnosis. Clinicians should be cautious in directly linking epilepsy to CA II deficiency. Bone marrow transplantation may be an effective treatment option for osteopetrosis in such cases. More research is recommended since the literature on this point is very scarce.

Keywords: Epilepsy, carbonic anhydrase II, seizures, osteopetrosis.

Introduction

The International League Against Epilepsy describes epilepsy as a chronic neurological disorder marked by the occurrence of two unprovoked seizures occurring more than 24 hours apart, or a single unprovoked seizure when the probability of a future seizure exceeds 60% [1]. Carbonic anhydrase (CA) is a crucial enzyme for the physiology of the brain, kidneys, and bones. This enzyme facilitates the synthesis of carbon dioxide and carbonic acid from water. Carbonic acid spontaneously dissociates to liberate protons, which are crucial for establishing the acidic environment necessary for the breakdown of bone minerals in the resorption lacunae [2].

Carbonic anhydrase II (CA II) deficiency is an uncommon condition resulting from a harmful mutation in the CA II gene, transmitted in an autosomal recessive pattern, and is characterized by a typical trio of renal tubular acidosis (RTA), osteopetrosis, and intracerebral calcifications [3]. Additional clinical manifestations, including developmental delay, cognitive impairments, cranial nerve compression, varied degrees of

Correspondence to: Anas Alamri
*Care Medical Hospital, Riyadh, Saudi Arabia.
Email: Alamri.anas@gmail.com
Received: 12 October 2025 | **Revised:** 23 November 2025 | **Accepted:** 24 December 2025

intellectual incapacity, and dental anomalies, are commonly related. Numerous mutations documented in the literature include the Arabic mutation (CA II c. 232 + 1 G > T) and the Egyptian mutation (CA II c. 191 del A), among others [4].

Recent research has recognized the importance of CA in epilepsy, establishing it as a promising target for the development of novel anticonvulsant medications [5]. CA II deficiency has a complex relationship with epilepsy; while it is hypothesized that CA II deficiency may increase resistance to seizures in animal models, it may also lead to a proconvulsant state *in vitro* by disrupting brain pH regulation, particularly in CA II-deficient brain slices. This dual effect highlights CA II's role in maintaining normal brain function and suggests that conditions leading to CA II deficiency, such as certain genetic disorders, may interact with the development of seizures [6]. Herein, we presented a known case of epilepsy who was diagnosed with it at the age of 12 years old, suffered osteopetrosis and basal ganglia, and we diagnosed her as a case of CA II deficiency at the age of 22 years old.

Case Report

The patient is a 22-year-old female with a history of intellectual disability and developmental delay. She experiences chronic bone pain and has frequent orthopedic visits due to recurrent fractures. She has a positive family history of seizure disorders, although no other known genetic diseases or parathyroid disorders were reported. She has no history of recent travel or previous surgeries.

She was diagnosed with epilepsy at the age of 12, presenting with absent-type seizures characterized by staring episodes lasting 2–3 minutes. These seizures occur without tonic-clonic movements, tongue biting, urinary incontinence, complete loss of consciousness, or identifiable auras. Despite treatment with Trileptal 900 mg and Keppra 1,500 mg, her seizures remained uncontrolled. During admission, she experienced two absent seizures lasting about 1 minute each, with altered consciousness and postictal confusion, but without tonic-clonic activity, urinary incontinence, or tongue biting.

The patient has a history of recurrent fractures at multiple sites, confirmed by X-ray examinations. She suffers from chronic bone pain and has been admitted

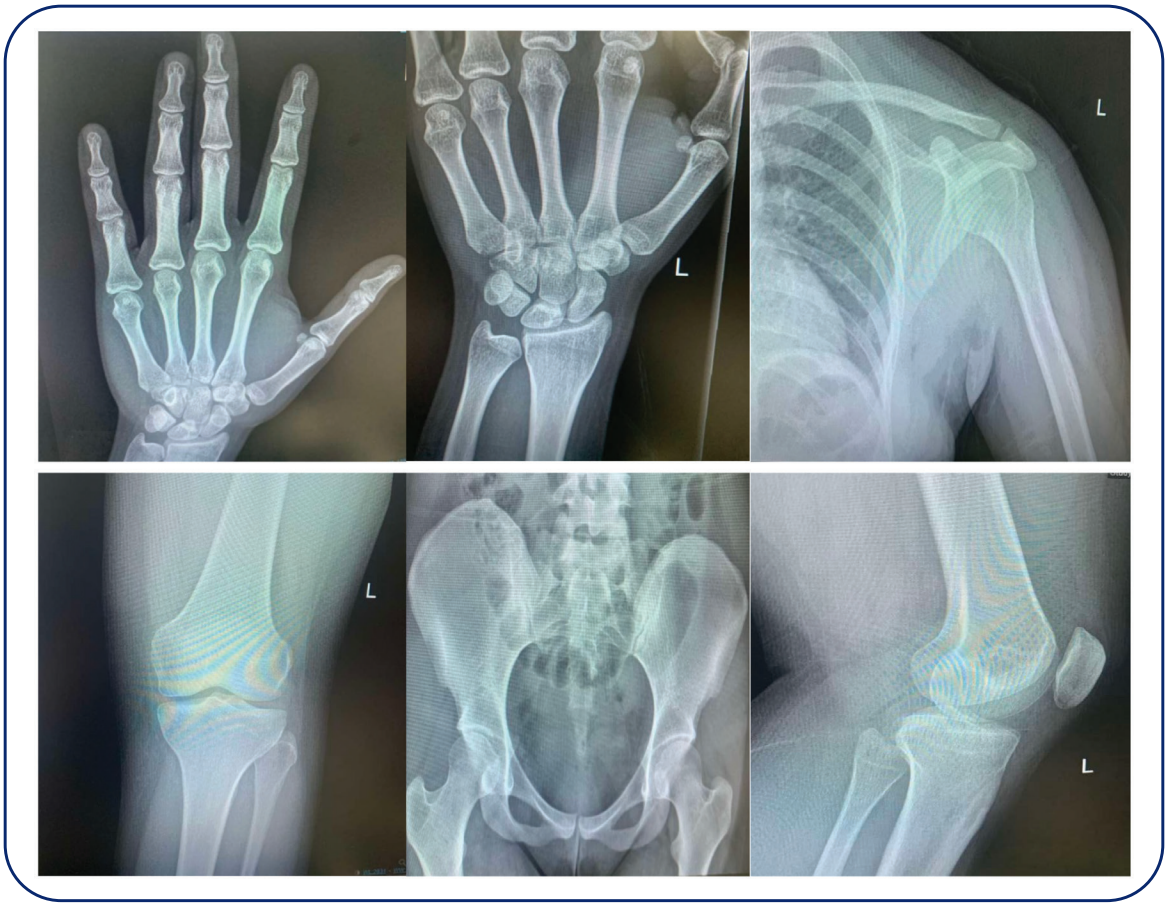

Figure 1. *Multiple X-ray examinations showed multiple fractures in different sites.*

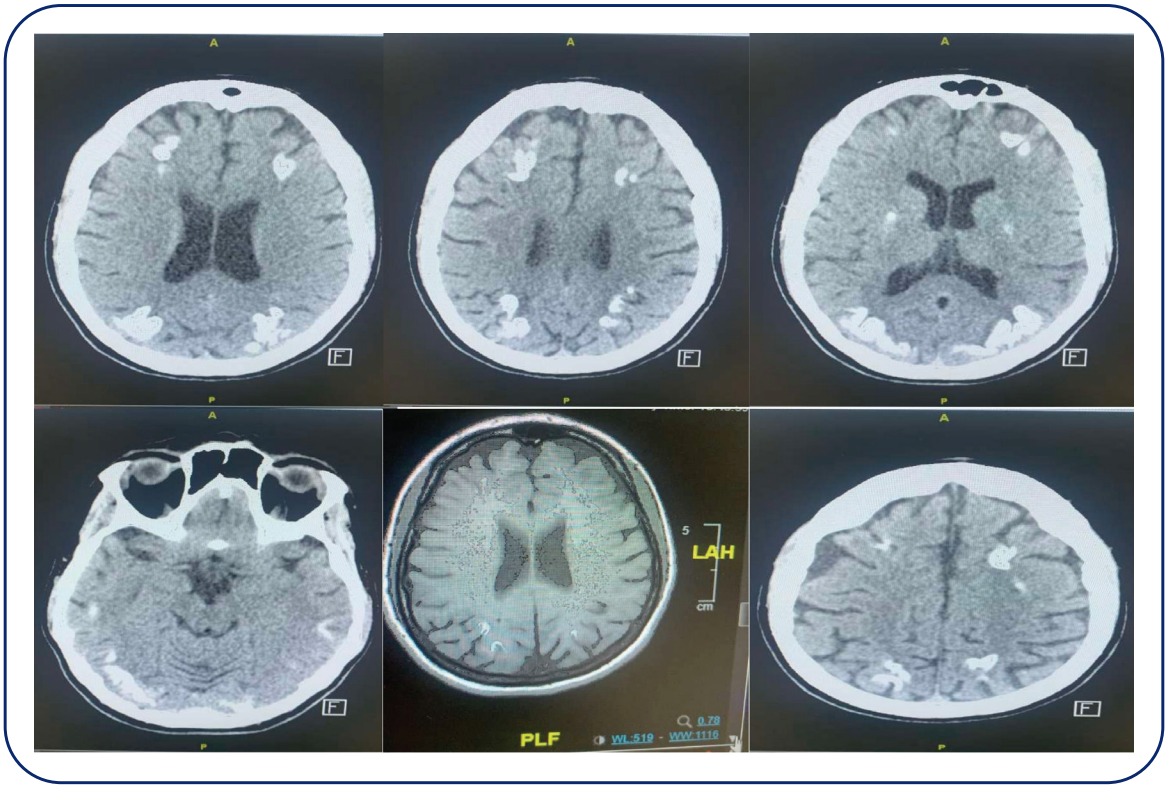

Figure 2. *CT scans showed calcification in the basal ganglia.*

multiple times for orthopedic evaluation and treatment. Imaging studies indicate osteopetrosis, consistent with her clinical presentation.

Laboratory investigations revealed hyponatremia (Na: 134 mEq/l; Normal range: 135-140 mEq/l) K: 3.4 mEq/l; Normal range: 3.5-5.2 mEq/l), and hypokalemia (She has a history consistent with mixed RTA due to CA II deficiency. Further metabolic evaluations, including bicarbonate levels and arterial blood gases, indicated her impaired acid-base balance.

Radiological assessments included multiple X-rays demonstrating fractures at different skeletal sites, confirming the presence of osteopetrosis (Figure 1). computed tomography (CT) scans of the brain revealed basal ganglia calcifications (Figure 2). Radiographic review indicates that the intracranial calcifications are consistent with the progression of CA II deficiency and are absent at birth, developing during childhood.

Genetic testing performed in Jordan confirmed CAII deficiency by identifying a mutation in the CA II gene. The specific variant, zygosity, and mutation class were consistent with the autosomal recessive inheritance pattern of the disorder, confirming the diagnosis.

Given the persistent uncontrolled seizures despite previous therapy, Keppra was discontinued, and Depakine 250 mg BID was initiated while maintaining Trileptal 900 mg BID. This adjustment was made to optimize seizure control, considering that CAII deficiency affects intracellular pH and may alter the efficacy of conventional antiepileptic drugs. The therapeutic approach aimed to enhance seizure responsiveness while managing the metabolic and skeletal complications associated with CAII deficiency.

Discussion

A. Clinical spectrum

Epilepsy is recognized as being linked to some inborn errors of metabolism (IEMs). IEMs should be considered, particularly in the presence of a positive family history, parental consanguinity, severe metabolic acidosis, developmental regression, developmental delay, dysmorphic features, failure to thrive, neurological abnormalities, and abnormal urine odor [7]. IEM abnormalities are linked to several seizure types. Seizures may manifest as the initial symptom or be provoked by concurrent illnesses and metabolic problems, including hypoglycemia. Nonetheless, spontaneous seizures or epilepsy have not been documented in CA II deficiency [8].

B. Osteopetrosis and the CA II pathway

CA II creates an acidic environment in the bone matrix by generating H+ ions through osteoclasts; hence, it facilitates bone resorption. A deficiency of CA II impedes bone resorption, disrupting the equilibrium between osteoblast and osteoclast activity, hence leading to

osteopetrosis [9]. CA II significantly contributes to the urine acidification in the distal collecting duct; its deficiency leads to distal RTA, although both proximal and distal forms may occur [10]. Herein, we presented a known case of epilepsy in a patient who was diagnosed with it at the age of 12 years old, and despite treatment with Trileptal and Keppra, seizures remained uncontrolled, leading to a diagnosis of CAII deficiency causing osteopetrosis and basal ganglia calcification.

CAII deficiency was first reported in 1972, and later characterized in Saudi families during the 1980s, where affected individuals showed mental impairment, growth retardation, dental anomalies, distinctive facial features, distal RTA, brain calcifications, and osteopetrosis. In 1983, CAII deficiency was identified as the underlying cause, explaining the presence of mixed RTA due to CAII expression in both osteoclasts and renal tubules [2]. The most common mutation is the so-called Arabic mutation, which involves the deletion of the splice donor site in intron 2 of the CAII gene [4]. Subsequent reports expanded the clinical spectrum to include hearing impairment, recurrent paralysis responsive to bicarbonate and potassium therapy, fractures, renal stones, and novel genetic mutations, with longterm follow-up studies documenting the biochemical, clinical, and radiological features in affected Saudi infants [2]. Hematological problems such as anemia, thrombocytopenia, and leukopenia are commonly observed in the recessive, fatal variant of osteopetrosis, although they are generally absent in osteopetrotic individuals with CAII deficiency [9]. Our case was an epileptic case with CAII deficiency complicated with osteopetrosis, where she was admitted to our hospital frequently with bone fractures at different sites.

C. Radiological features

Intracranial calcification, including the basal ganglia and the periventricular and subcortical white matter, is a constant manifestation of this disease. The mechanism of cerebral calcification is unclear, and the function of the CAII enzyme in the brain is unknown [10]. Ohlsson et al. [11] reviewed the radiographs of 16 Saudi children with this syndrome and showed that calcification is not present at birth but usually appears after the 2nd year of life and increases in density and extent through childhood. Cranial nerve encroachment on neuronal foramina was reported in 6 of 21 patients by Sly and Hu [9]. Optic nerve atrophy has also been described in patients with normal-sized optic foramina, with an unclear underlying mechanism [12]. Regarding our case, the CT scans reported basal ganglia calcification.

D. Genetic variants

CA II is an enzyme encoded by the CA II gene on chromosome 8q22, and its lack results in an autosomal recessive disease. It is characterized by a single α-CA domain and is extensively distributed in red blood cells, the kidney, bone, and brain [13].

CA II deficiency is diagnosed clinically by symptoms like bone fractures, growth failure, and mental disability, supported by radiological findings of osteopetrosis and cerebral calcification, and definitively confirmed by molecular testing to identify mutations in the CA II gene. Biochemical testing can show reduced CA II in blood cells, which, combined with the clinical picture and genetic analysis, leads to a diagnosis of this rare autosomal recessive disorder [13]. Regarding our case, she suffered bone fractures, developmental delay, delayed progress in school, osteopetrosis, and calcification in the basal ganglia. The genetic analysis confirmed CA II deficiency.

E. Epilepsy and the CA II pathway

Regarding the association between epilepsy and CA, previous studies assumed a potential role for CA in the pathogenesis and treatment of epilepsy. They proposed that antiepileptic drugs may function through a dual mechanism: first, by affecting Na+ channels, Ca2+ currents, or the GABA system; and second, by inhibiting CA, thereby increasing pH levels [14]. These pH increases could be significant in the intracellular mechanisms of antiepileptic drugs. Conditions like cerebral edema and hypoxia enhance neuronal excitability, causing alterations in pH and CO_2 levels that may contribute to epilepsy [14]. Regarding our case, by chance, she suffered inherited CA II deficiency, which caused increasing pH levels, which is significant in the intracellular mechanisms of antiepileptic drugs, and can cause an increase in the response to the anti-seizure drugs.

F. Treatment options

Recent reports indicate that bone marrow (BM) transplantation contributes to the histological and radiological resolution of osteopetrosis in these cases. Allogenic BM stem cell transplantation was successfully conducted in two Irish infants with this disease, which impeded the progression of cerebral calcification; nevertheless, it had no impact on RTA and cognitive impairment [15].

Conclusion

This case is a rare case of epilepsy associated with CA II deficiency, a rare genetic disorder, with novel co-occurrence of osteopetrosis. It emphasizes the importance of considering CA II deficiency in patients with unexplained bone and brain abnormalities and recommends genetic testing to confirm the diagnosis. Clinicians should be cautious in directly linking epilepsy to CA II deficiency. Bone marrow transplantation may be an effective treatment option for osteopetrosis in such cases. More research is recommended since the literature on this point is very scarce.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Due permission was obtained to publish the case and the accompanying images.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Anas Alamri[1]

1. Care Medical Hospital, Riyadh, Saudi Arabia

References

1. Definition of Epilepsy 2014. International league against epilepsy. [cited 2021 Jun 30]. Available from: https://www.ilae.org/guidelines/definition-and-classification/definition-of-epilepsy-2014
2. Alsharidi A, Al-Hamed M, Alsuwaida A. Carbonic anhydrase II deficiency: reported a novel mutation. CEN Case Rep. 2016;5(1):108–12. https://doi.org/10.1007/s13730-015-0205-y
3. Whyte MP. Carbonic anhydrase II deficiency. Bone. 2023;169:116684. https://doi.org/10.1016/j.bone.2023.116684
4. Lotan D, Eisenkraft A, Jacobsson JM, et al. Clinical and molecular findings in a family with the carbonic anhydrase II deficiency syndrome. Pediatr Nephrol. 2006;21:423–6. https://doi.org/10.1007/s00467-005-2125-0
5. Ozsoy HZ. Anticonvulsant effects of carbonic anhydrase inhibitors: the enigmatic link between carbonic anhydrases and electrical activity of the brain. Neurochem Res. 2021;46:2783–99. https://doi.org/10.1007/s11064-021-03390-2
6. Velíšek L, Moshé SL, Stanton PK. Increased susceptibility of brain slices from carbonic anhydrase II-deficient mice to low [Mg2+] 0-induced seizures. Neurosci Lett. 1996;207(3):143–6. https://doi.org/10.1016/0304-3940(96)12515-5
7. Papetti L, Parisi P, Leuzzi V, Nardecchia F, Nicita F, Ursitti F, et al. Metabolic epilepsy: an update. Brain Dev. 2013;35(9):827–41. https://doi.org/10.1016/j.braindev.2012.11.010
8. Urmila NM, Kewalramani D, Balakrishnan U, Manokaran RK. A case of carbonic anhydrase type VA deficiency presenting as West syndrome in an infant with a novel mutation in the CA-VA gene. Epilepsy Behav Rep. 2022;20:100573. https://doi.org/10.1016/j.ebr.2022.100573
9. Sly WS, Hu PY. The carbonic anhydrase II deficiency syndrome: osteopetrosis, renal tubular acidosis and cerebral calcification. In: Scrivers CR, Beaudet AL, Sly WS, editors. The metabolic and the molecular bases of inherited diseases. 7th ed. Columbus, OH: McGraw Hill; 1995. pp 4113–24.
10. *Batlle D, Haque SK. Genetic causes and mechanisms of distal renal tubular acidosis. Nephrol Dial Transplant. 2012;27(10):3691–704.* https://doi.org/*10.1093/ndt/gfs442*
11. Ohlsson A, Cumming WA, Paul A, Sly WS. Carbonic anhydrase II deficiency syndrome: recessive osteopetrosis with renal tubular acidosis and cerebral calcification. Pediatrics. 1986;77:371–81. https://doi.org/10.1542/peds.77.3.371
12. Cochat P, Loras-Duclaux I, Guibaud P. Deficit en anhydrase carbonique II: osteopetrose, acidoserenaletubulaire et calcifications intracraniennes. Revue de la literature a partir de trois observations. Pediatrie. 1987;47:121–4.
13. Al Zouabi SS, Abdulla MC, Amer MS. Renal tubular acidosis, osteopetrosis, and cerebral calcification triad of carbonic anhydrase II deficiency. Case Rep. 2024;6(2):149–52. https://doi.org/10.1111/epi.16715
14. Singh T, Joshi S, Williamson JM, Kapur J. Neocortical injury-induced status epilepticus. Epilepsia. 2020;61:2811–24. https://doi.org/10.1111/epi.16715
15. McMahon C, Will A, Hu P, Shah GN, Sly WS, Smith OP. Bone marrow transplantation corrects the osteopetrosis in the carbonic anhydrase II deficiency syndrome. Blood. 2001;97:1947–50. https://doi.org/10.1182/blood.V97.7.1947