

CASE REPORT

Carbonic anhydrase II deficiency presenting as refractory absence epilepsy with osteopetrosis and basal ganglia calcification: a case report

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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 (CA) is a crucial enzyme in physiological functions. CA II deficiency is a rare autosomal recessive disorder caused by mutations in the CA2 gene, which is mainly characterized by osteoporosis. Recent research highlights the complex relationship between CA II and epilepsy; while CA II deficiency may provide resistance to seizures in animal models, it can also provoke seizures by disrupting brain pH regulation. 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. Herein, we presented a rare case of 22 years old female who had a history of epilepsy, and recently, she was diagnosed with CAII inherited deficiency, which caused osteopetrosis and, consequently, multiple bone fractures.

Case presentation: 22-year-old female with a history of absent seizures presented to the emergency room 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 carbonic anhydrase II deficiency causing osteopetrosis and basal ganglia calcification. The treatment plan included stopping Keppra and initiating Depakin while maintaining Trileptal dosage. Gene testing confirmed CAII deficiency.

Conclusion: This case highlights the importance of considering CA II deficiency when osteopetrosis and cerebral calcification occur together. The available information does not establish that CA II deficiency caused the patient's seizure episodes. Further clinical, biochemical, electroencephalographic, and molecular details are needed to characterize the epilepsy phenotype and assess possible contributing factors.

Keywords: Epilepsy, Carbonic anhydrase II, seizures, osteoporosis.

Introduction

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 [1]. CA II (CA II) deficiency is an uncommon condition resulting from a harmful mutation in the CA2 gene,

transmitted in an autosomal recessive pattern, and is characterized by a typical trio of renal tubular acidosis (RTA), osteopetrosis, and intracerebral calcifications

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[2]. Additional clinical manifestations, including developmental delay, cognitive impairments, cranial nerve compression, varied degrees of intellectual incapacity, and dental anomalies are commonly related. Numerous mutations documented in the literature encompass the Arabic mutation (CA 2 c. 232 + 1 G > T), the Egyptian mutation (CA 2 c. 191 del A), among others [3].

CAs have been studied in relation to neuronal excitability and antiseizure drug mechanisms. However, experimental findings concerning CA II deficiency and seizure susceptibility are not consistent, and epilepsy is not established as a defining feature of CA II deficiency [4,5]. We describe a young woman with reported genetically confirmed CA II deficiency, osteopetrosis, cerebral calcification, and longstanding seizure episodes. Because important diagnostic details were unavailable, the relationship between the metabolic disorder and the seizures is discussed cautiously.

Case report

A 22 years old female, known case of absent seizure on oral medication, presented to emergency room after felt down on her left side with multiple bruises after an episode of convulsion. She had a history of recurrent attack of seizure even with medication. She was diagnosed with epilepsy at the age of twelve years old. No change in the pattern, each attack lasting 2–3 minute, described as staring with no tonic clonic convulsion. No tongue pitting or urine incontinence, no complete loss of consciousness, and no precipitating factor or aura. She suffered intellectual disability with developmental delay and delay progress in the school. Depression was not on medication. She had a history of trauma with each attack, and chronic bone pain with frequent orthopedic visits. Other systemic reviews were unremarkable except for chronic bone pain. She had a positive family history of seizure disease, no genetic

disease, no history of parathyroid disease, no recent travel, and no history of previous surgery (Table 1).

She was sitting on the bed for clinical examination, she was connected to intravenous (IV) normal saline (NS), and she was confused but responding. She suffered two attacks lasting about 1 minute of absent seizure during examination with altered conscious level, no tonic clonic movement, no urinary incontinence or tongue biting, and the post ictal was also confused. During the attack the vital signs were; blood pressure (BP) 120/70, heart rate (HR) 50, temperature 37.0, respiratory rate (RR) 18, and oxygen saturation (SPO₂) 96% on room air.

Head, eyes, ears, nose, and throat examination showed; no eye protrusion, no pallor or jaundice, normal mouth hydration, no central cyanosis or ulcer, no deformity or nasal discharge, and multiple red bruising on the left side of the face. Neck, hand, and lower limb examinations were normal except for multiple scars and bruising in the left arm, hand, and left leg.

The central nervous system (CNS) examination showed intellectual disability, and the central vascular (CVS) examination was normal. All other systems unremarkable, except multiple bruises on the skin.

The laboratory investigations reported hyponatremia (Na: 134; normal 135 to 145 mEq/l), and hypokalemia (K: 3.4; normal 3.5 to 5.0 mEq/l).

She was on Trileptal 900 mg, and recently, keppra 1500 mg BD with Oxcarbazepine was added. After one week one this treatment, she stilled uncontrolled seizure, and she suffered recurrent fracture and chronic bone pain. Depending on multiple X-rays (Figure 1) and neurology consultation, the final impression was carbonic anhydrase II (CAII) deficiency causing osteopetrosis with calcification in the basal ganglia, which reported in computer tomography (CT) scans (Figure 2).

Table 1. Clinical timeline

Time point	Documented event
Age 12 years	Seizure episodes began; the patient was diagnosed with epilepsy according to the history.
Over subsequent years	Episodes reportedly continued, described as staring with altered awareness and lasting about 2–3 minutes. Developmental delay/intellectual disability and chronic bone pain were reported; recurrent fractures/trauma led to orthopedic visits.
Current presentation, age 22 years	Presented after a fall associated with an episode described as a convulsion; two staring episodes with altered awareness were observed during examination.
Initial investigations	Sodium 134 mEq/l and potassium 3.4 mEq/l. Imaging was reported to show osteopetrosis and basal ganglia calcification. Detailed EEG, brain-imaging report, and RTA-related biochemical results were not available in the manuscript.
Genetic evaluation	CA II deficiency was reported as confirmed by testing performed in Jordan; exact variant and laboratory details were not provided.
Medication change	Levetiracetam was stopped, valproate 250 mg twice daily was started, and oxcarbazepine 900 mg twice daily was continued.
Follow-up	Duration of follow-up and seizure outcome after the medication change was not documented.





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

The treatment plan was stopping Keppra, starting Depakin 250 mg BID, and keeping Trileptal 900 mg BID.

CAII gene tests were done in Jordan on which confirm the diagnosis with CAII deficiency.

Discussion

CA II is an enzyme encoded by the CA2 gene on chromosome 8q22, and its lack results in an autosomal recessive disease [6]. It is a zinc-dependent metalloproteinase that facilitates the reversible conversion of CO₂ and bicarbonate (HCO₃⁻), resulting in the release of H⁺ ions into the bloodstream and other bodily tissues [7]. CA II is among the most enzymatically active types, characterized by a single α-CA domain, and is extensively distributed in red blood cells, kidney, bone, and brain. It assists in preserving acid-base equilibrium in tissues and blood. It creates an acidic environment in the bone matrix by generating H⁺ ions through osteoclasts, hence facilitating bone resorption. A deficiency of carbonic anhydrase II impedes bone resorption, disrupting the equilibrium between osteoblast and osteoclast activity, hence leading to osteopetrosis [8]. 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 [9]. Herein, we presented a known case of epilepsy who 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.

The syndrome was first described in the early 1970s, and subsequent studies in Saudi families established the association between CAII deficiency and its characteristic clinical and radiological features. A common pathogenic variant, known as the Arabic mutation, affects the splice donor site in intron 2 of the CAII gene. Later reports have expanded the clinical spectrum to include hearing impairment, recurrent episodes of acute paralysis, bone fractures, and renal calculi. Long-term follow-up studies have also provided further insight into the biochemical, clinical, and radiological manifestations of this condition [10]. Our case was epileptic case with CAII deficiency complicated with osteopetrosis where she admitted to our hospital frequently with bone fractures at different sites.

Intracranial calcification including the basal ganglia and the periventricular and subcortical white matter is a constant manifestation of this disease. The cerebral calcification mechanism is unclear and the function of CAII enzyme in the brain is unknown [11]. Optic nerve atrophy has been also described in patients in whom the optic foramina were of normal size with unclear



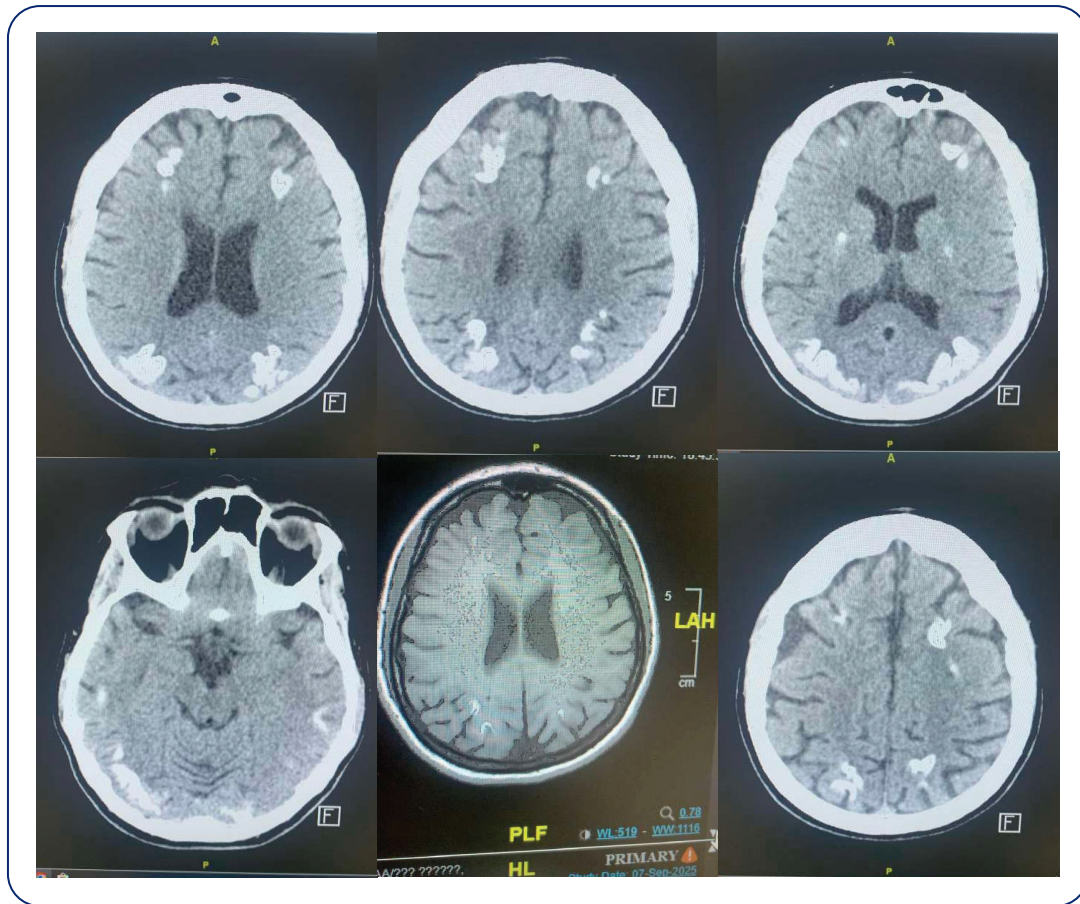


Figure 2. Brain CT reported to show intracranial calcification, including the basal ganglia. The full distribution and extent of calcification should be verified against the original radiology report before submission.

underlying mechanism [12]. Hepatosplenomegaly and deafness and hydrocephalus anemia were described in Arabic cases with this syndrome from Kuwait and Saudi Arabia [8, 10]. Regarding our case, the CT scans reported basal ganglia calcification.

CAII deficiency is diagnosed clinically by symptoms such as bone fractures, growth failure, and mental retardation, supported by radiological findings of osteopetrosis and cerebral calcification, and definitively confirmed by molecular testing to identify mutations in the CA2 gene. Biochemical testing can show reduced CAII 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 and delay progress in the school, osteopetrosis, and calcification in the basal ganglia. The genetic analysis confirmed CAII deficiency.

Regarding the association between epilepsy and carbonic anhydrase, studies indicate that patients with epilepsy exhibit elevated CA activity in red blood cells compared to controls, with serum from these patients activating purified CA, an effect inhibited by proglumid

and cimetidine. These results assumed a potential role for CA in the pathogenesis and treatment of epilepsy. The current study proposes that antiepileptic drugs may function through a dual mechanism: first, by affecting Na^+ channels, Ca^{2+} currents, or the GABA system, and secondly, by inhibiting CA which leads to increased 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. Furthermore, decreasing the concentration of CA II via antiepileptic medication can help mitigate the frequency and seizures intensity. CA, a glial enzyme, links glucose metabolism, neuronal loss, and brain atrophy with epilepsy. This dual action offers insights into the anticonvulsant properties of commonly used drugs such as carbamazepine and phenytoin, highlighting that the regulation of glial cell activity through CA inhibition may play a vital role in maintaining acid-base balance and limiting seizure propagation [14]. Regarding our case, by chance she suffered inherited CAII deficiency, which causing increasing pH levels, which is significant in the intracellular mechanisms of



antiepileptic drugs, and which can cause increasing the response to the anti seizures drugs.

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].

The principal limitations are the incomplete clinical and diagnostic record. The available manuscript did not include EEG results, a detailed neurology assessment, the complete brain-imaging report, the exact CA2 variant and laboratory method, family segregation testing, or the biochemical data needed to evaluate RTA. Anthropometric measurements, growth trajectory, detailed dental findings, renal manifestations, hearing and visual assessment, and parental consanguinity or a fuller family history were also not reported. The precise fracture sites and radiographic findings, the rationale for the antiseizure medication change, and the duration and outcome of follow-up were unavailable. These omissions limit assessment of the seizure classification, confirmation of the full CA II deficiency phenotype, and evaluation of any causal association between the disorder and the seizures. The findings should therefore be interpreted as a reported coexistence of CA II deficiency, osteopetrosis, cerebral calcification, and seizure episodes rather than proof that CA II deficiency caused epilepsy.

Conclusion

This case emphasizes the diagnostic importance of recognizing osteopetrosis and cerebral calcification in a patient reported to have CA II deficiency. The available record does not fully document RTA or characterize the seizure episodes sufficiently to confirm absence epilepsy or drug-resistant epilepsy. Nor does it establish a causal relationship between CA II deficiency and the seizures. Complete biochemical, electroencephalographic, radiological, and molecular documentation, together with longitudinal follow-up, is needed to clarify the phenotype and guide interpretation.

Conflict of interests

The authors declare that they have no competing interests.

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Consent for participate

The patient gave written informed consent for publication of this study and related images.

Ethics approval

Ethical approval and patient consent were obtained according to the rules of the participating institution.

Availability of data and materials

The text contains all related radiological and clinical data supporting this case report.

Authors' contributions

All authors contributed to clinical data collection, manuscript preparation, critical revision, and approval of the final version of the manuscript.

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