



AFGHAN MUTATION OF CA-II GENE; OSTEOPETROSIS AND CARBONIC ANHYDRASE II DEFICIENCY WITH CRANIOFACIAL DISPROPORTION IN AN AFGHAN CHILD

Dr Anila Faisal¹, Dr Amarah Kiani², Dr Ahsen Farooq³

1. (MBBS, FCPS)
Assistant Consultant, Radiology
Department
Quaid E Azam international hospital
Rawalpindi
2. (MBBS, FRCR 2A) Radiologist QIH
3. (MBBS, FCPS)
Head of Radiology Department QIH
Rawalpindi

Correspondence Address:

Dr Anila Faisal
H # 370 D, St# 18 A,
Ghori Town phase 4A, Islamabad.
dr.talpur@hotmail.com

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ABSTRACT: Carbonic anhydrase-II deficiency is an autosomal recessive disorder grounded on a triad of cerebral calcification, osteopetrosis and renal tubular acidosis away in which proximal tubules, distal collecting ducts or combined.¹ Other features include growth and mental retardation along with the complications of osteopetrosis.² The only treatment to cure the calcification is allogeneic bone marrow stem cell replacement; however it does not have any considerable effect on the renal lesions³ We report a case of a 3 week old male child of Afghan origin with all these features who was clinically diagnosed as having carbonic anhydrase type II deficiency however unfortunately the baby passed during cranioplasty and genetic testing for enzyme deficiency could not be done. Our aim to present this case of a male child of Afghan origin is to enhance the awareness about this rare syndrome in our medical community and inviting further research for a possible Afghan mutation of CA-II gene.

Key words: craniofacial disproportion, carbonic anhydrase II gene. Osteopetrosis.

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INTRODUCTION

Guibaud-Vainsel syndrome or marble brain disease was first described in 1972. In these patients the activity of carbonic anhydrase II (CAII) in erythrocytes was absent, signifying that this was the primary deficiency.² Carbonic anhydrase-II enzyme (CA-II) is involved in the reversible hydration of carbon dioxide to form carbonic acid (H_2CO_3). It is generally circulated in bones, kidney, red blood cells and glial cells. CA-II is abundant in Osteoclasts. Deficiency of CA-II enzyme leads to compromised production of H^+ by the osteoclasts and, to produced defective bone resorption and finally causing osteopetrosis.³

The CA gene has been identified and is situated on chromosome 8¹⁻⁴. Twelve known mutations of the CAII gene have been recognized. But, 3 mutations (His107Tyr, 2971G3a, and 744delA) are liable for more than 90% of the cases of CAII deficiency.⁴

CA-II deficiency is commonly found in the Gulf States and Arab population, this type of disease is known as Arabic mutation, and it is also

reported in American, Belgium and Japan.¹ Our patient apparently is the first case in the afghan population to be document.

In this study we report the case, who presented with craniofacial asymmetry, widely patent sutures and classical triad of cerebral calcification, renal tubular acidosis, osteopetrosis diagnosis as CA II deficiency. As the patient could not be followed up so it was not possible to comment on developmental delay or mental retardation.

CASE REPORT

A 21 day old male baby born at a hospital in Kabul Afghanistan following an uneventful C section after an uncomplicated pregnancy. His birth weight was 2.8 kg. He was brought to our hospital Quaid e Azam international hospital for correction of his craniofacial disproportion. Family history was revealed that the baby had one brother and one sister and both of them had no medical issues. In the past history of patient, CT scan was previously done at 6 days of age which shows mild subarachnoid hemorrhage along with mild diffuse brain edema and sub endymal

calcifications.

On physical examination baby was found to be weighing approximately 3.0 kg (< 5th percentile) measuring about 43cm in length (< 5th percentile) with a head circumference of 33cm (<5th percentile). He had dysmorphic features with craniofacial disproportion. All the skull sutures were widely open with a broad prominent forehead and depressed nasal bridge (figure-1). Marked bilateral proptosis was noted with bulging wide set eyes and the baby was unable to completely close his eyelids.



Figure-1. Craniofacial disproportion with hypertelorism, proptosis, broad prominent forehead, depressed nasal bridge.

Systemic examination revealed hepatosplenomegaly but otherwise soft with positive bowel sound. Baby was taking feeds normally maintaining his blood oxygen saturation satisfactorily and was in no apparent distress. A referral to the neurosurgical team was made for the arrangement of corrective surgery in order to decompressing the ventricles, widening of the anterior cranial fossa and to reduce the proptosis and eliminate the forthcoming threat to the eye sight caused by severe proptosis.

Routine blood tests were advised along with a chest x ray and a CT of face and brain with 3D reconstruction

Laboratory examination yielded the following: hemoglobin 11.6 g/dl; Red blood cells count 3600 cells /mm³ white blood cell count 7600 cells/mm³ and platelet count 50,000/mm.³ Biochemical analysis was normal except for AST 47 U/L, low Albumin 2.7.

Plasma biochemistry revealed plasma glucose 90mg/dl plasma creatinine 0.33, plasma sodium 144, plasma potassium 2.4, plasma chloride 105, and plasma bicarbonate 30. Urine Ph was 5.0.

A chest x ray AP view revealed diffusely increased bone density of all the visualized bones including the rib cage, humeri, thoracic spine. Heart size was normal and No parenchymal lung abnormality was detected (figure-2).



Figure-2. Chest x ray showing diffusely increased density of all the bones. Vertical leucient lines in the ribs bilaterally give the typical appearance of “Bone in bone”.

A computed axial tomographic scan of the face and brain revealed thick calvarium with obliterated marrow space. Multiple foci of calcification are seen in the periventricular regions and basal ganglia bilaterally. Mild hydrocephalus was noted with dilatation of the temporal horns of the lateral ventricles. It also showed shallow anterior cranial fossa, narrow orbital cavity, broad prominent forehead and widely patent sutures. Intersutural distance was approximately 43mm with multiple wormian bones (figure-3).

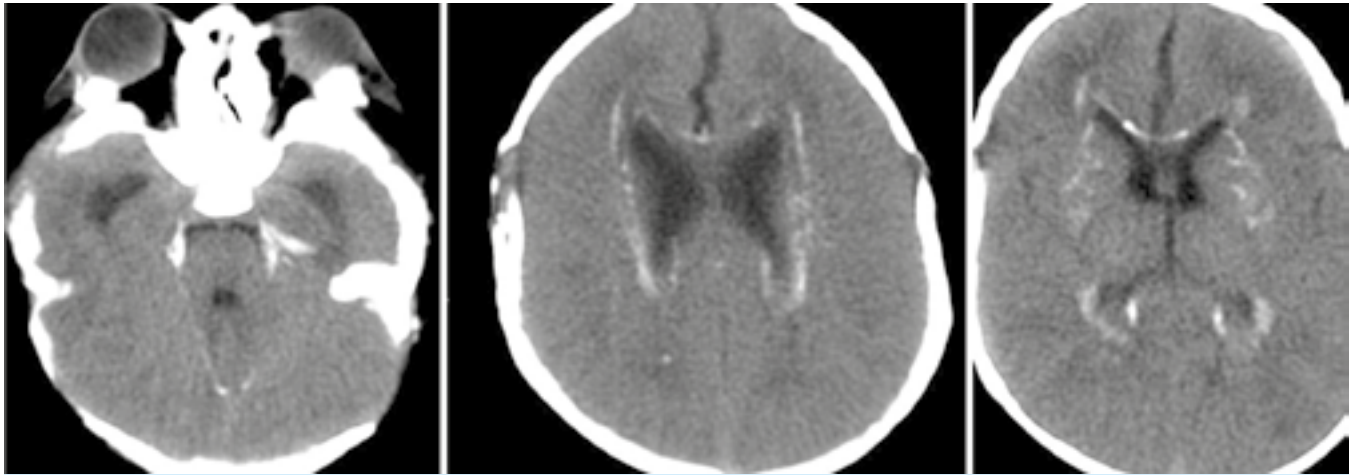


Figure-3.

(a) Non contrast enhanced CT Brain axial view shows proptosis and shallow anterior cranial fossa along with dilated temporal horns of the lateral ventricles, increased density of the calvarium.

(b-c) CT brain with contrast axial view shows periventricular calcification along with bilateral basal ganglia calcifications.

These findings led to the suspicion of CA II deficiency syndrome and further tests were advised including an abdominal ultrasound in which there was mild hepatosplenomegaly with bilaterally medullary calcifications (medullary nephrocalcinosis).

Unfortunately, both proper genetic-testing or erythrocyte lysate test are not available in our center, and a clinical diagnosis of CA-II deficiency was made. A cranioplasty was planned but unfortunately baby suffered a cardiac arrest soon after the administration of the general anesthetic and could not be revived.

DISCUSSION

CA-II deficiency is also known as marble brain disease. It is a clinical diagnosis based on the manifestation of cerebral calcification, osteopetrosis and renal tubular acidosis. It is mainly inherited as autosomal recessive type; however, autosomal dominant type has been reported as well.¹

The facial features of CAII deficient patients include large cranial vault, broad forehead, short stature, craniofacial disproportion and developmental delay⁵. In our patient the baby has prominent craniofacial disproportion, proptosis which is unusual in this syndrome and somewhat

rarely seen.

During chest x-ray reporting of our patient, there was incidental finding of osteopetrosis and on CT brain marked peri ventricular and intracranial calcifications with mild hydrocephalus was present. CT with 3D reformat was basically done in our patient for the purpose of corrective surgery of proptosis.

In the case report of Nampoothiri S³ showed that in CAII deficiency intracranial calcifications are mostly occur by 2-5 years of age. But in our patient with the age of less than one month intracranial calcifications was present. Pathogenesis of the cerebral calcifications is still unclear. They are noted mostly in basal ganglia.³

All these findings increased our key of thought about the diagnosis of carbonic anhydrase type II deficiency. So ultrasound abdomen was planned which showed medullary nephrocalcinosis and hepatosplenomegaly. With the help of ultrasound and laboratory findings diagnosis of renal tubular acidosis was established and hence the triad was complete. Unfortunately, both proper genetic-testing or erythrocyte lysate test are not available in our center, and a clinical diagnosis of CA-II deficiency was made. Unfortunately during corrective surgery of proptosis baby was suffered by cardiac

arrest soon after the administration of the general anesthetic and could not be revived.

The first differential diagnosis was malignant infantile osteopetrosis (MIOP). It is an autosomal recessive disorder characterized by impaired activity of osteoclasts together with normal bone formation by osteoblasts finally leads to the development of dense but fragile sclerotic bones.⁶ MIOP presents within the first few months after birth with sclerotic bones. Due to over growth of cranial nerve foramina causing compression of nerve, commonly affects the optic, facial and auditory nerves. Other features include extra medullary hematopoiesis resulting in hepatosplenomegaly, anemia, and thrombocytopenia. Recurrent infections and growth retardation may also be seen. This disease is usually fatal in infancy.⁷ Intracranial calcifications and renal tubular acidosis is not seen in these patients, however in our patient these two are the key manifestations.

The other differential diagnosis of crouzons disease was made on the basis of cranio facial asymmetry and exophthalmos which was almost always present⁸, as in our patient, although the facial features were suggestive, however craniosynostosis was not seen which is typical of crouzons.

A carbonic anhydrase 2 deficiency is a rare but important diagnosis that is base on the clinical manifestation. It should be considered in any patient who presenting with features of renal tubular acidosis, osteoporosis and intracranial calcifications. Finding of one of the features should

initiate a search for the other two components of this syndrome.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr Anila Faisal		
2	Dr Amarah Kiani		
3	Dr Ahsen Farooq		