CASE REPORT

Adenosine Kinase Deficiency Symptoms, Effects and Outcome in a 9-Year-Old Girl

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Pak Pediatr J 2025; **49(1):** 96-101

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Received 5th August 2024;
Accepted for publication 20th January 2025

ABSTRACT

Adenosine kinase deficiency (ADK) is an autosomal recessive disorder of methionine metabolism which results in elevated methionine levels and liver damage. Effected child has dysmorphic features and is developmentally delayed due to central nervous system involvement. Repeated jaundice and URTIs are commonly reported symptoms.

The disease needs to be confirmed through genetic analysis and diagnosed cases can be offered methionine free diet as the only known treatment option which does not result in complete recovery; however, it can sometimes improve liver functions and overall quality of life.

A case of 9-year-old Pakistani girl is reported with characteristic features of ADK deficiency, she was developmentally delayed, had tall stature, Developmental dysplasia of the hip (DDH), muscular hypotonia, epilepsy and hepatic dysfunction along with some rare features not commonly found in other reported cases. She worsened over one month period and passed away due to decompensated liver disease.

This report would help the clinicians decide when the testing for ADK deficiency is required, and how an early diagnosis can control the worsening of symptoms and prolong life expectancy.

Key Words: Methionine, Adenosine kinase – ADK – deficiency, Developmental delay, Adenosine

INTRODUCTION

Adenosine kinase deficiency (ADK) OMIM: 614300 is an autosomal recessive disorder of methionine metabolism, it is caused by homozygous mutation in ADK gene on chromosome 10q22.[1] The mutation was first identified by Bjursell et al in 2011 who tested it on 2 siblings of a Swedish family. Total of 27 cases have been reported so far from different countries including Sweden, Germany, Turkey, Malaysia, Saudi Arabia and Iran.[2] Adenosine kinase is used for phosphorylation of adenosine to adenosine monophosphate (AMP). 5' neuclotidase can be used to dephosphorylate it back to adenosine. This cycle balances adenosine and adenosine nucleotide levels.

Hypermethionemia can be used as a biomarker of inherited inborn error of metabolism that involves methylation cycle including MAT I/III deficiency, glycine N-methyltransferase deficiency, SAH hydrolase deficiency, and homocystinuria due to CBS deficiency.[2,3] There can be some indirect causes as well including mitochondrial disorders and some other causes including liver disease.

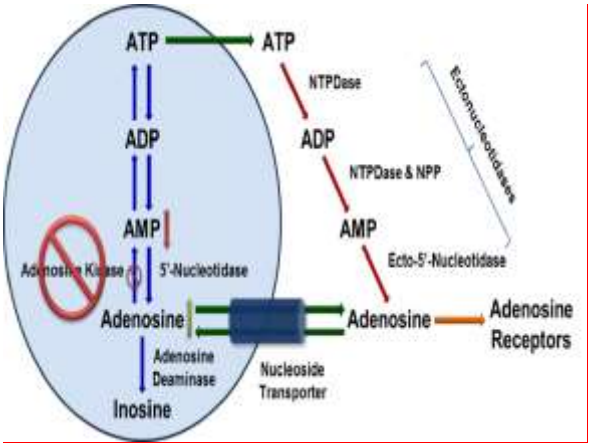

Fig1: Adenosine kinase inhibition

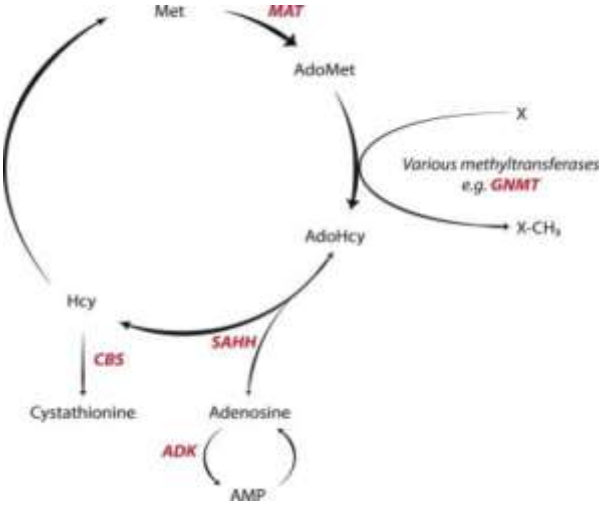

Fig 2: The methionine cycle

Clinical features include delayed developmental milestones, decreased muscle tone, dysmorphic features (frontal bossing, low set ears), early onset seizures (epilepsy) and liver dysfunction.

Ursula Sandau and Colino-Oliveira performed a study on mice and proved that brain wide disruption of ADK results in spontaneous seizures and learning impairment.[5]

Cardiac abnormalities are also reported in some patients. Liver enzymes are often elevated along with bilirubin. Plasma amino acid levels show markedly elevated methionine and slightly raised homocysteine levels. MRI brain would show delay in myelination and some white matter changes. Diagnosis is confirmed through genetic testing, when pathogenic variants in ADK gene have been inherited from both parents.

Methionine restricted diet is the only known treatment option which in previous cases did not show any significant effect on child's health.[2] To improve the outcome there should be regular check on liver functions and seizures, if present, should be controlled by drugs. There is no cure of the disease till date and all the treatments are to improve the quality of life.[2,4]

We report a 9-year-old Pakistani girl of ADK deficiency, her clinical features, laboratory findings and given treatments.

CASE REPORT

This case reports a 9-year-old girl who was third born child of parents who has a consanguineous marriage and their first two children are normal. She was delivered via elective caesarean section on July 27, 2015 due to previous two caesarean sections. She was delivered at full term (38 weeks) with APGAR of 8/10 and 10/10 at 1 and 5 minutes and birth weight of 2.8 kg. Pregnancy was uneventful and baby was immediately handed over to parents with no congenital or other health problems.

She developed jaundice for the first time in September 2015 at 2 months of age and had elevated liver enzymes (ALT>3000) at the time, after which she had multiple episodes of prolonged severe jaundice secondary to respiratory tract infections and gastric infections (on average twice a month) which sometimes required hospital admissions. It was first noticed at 4 months of age that she had poor sucking and neck holding and had mild delay in milestones, she had her first MRI scan done on 27th of May 2016, at 10 months of age which showed delay in myelination. Dr. Shoaib Ahmed, her primary consultant at the time, raised the concern about genetic screening for the first time after MRI report but it could not be done at the time.

She had her hearing tests (otoacoustic emissions), eye examinations and echocardiography done in 2017 due to delay in milestones, which were normal however BERA showed mild hearing loss. She could not walk, sit

without support, hold her head or eat and had poor swallowing at the time.

She also had developmental dysplasia of right hip joint for which she had corrective surgery on 17th of April, 2017. She was referred for speech and physiotherapy by her pediatrician and it showed no improvement after multiple sessions.

During her acute respiratory illness she had her first seizure in November 2019, at 4 years of age, after which she started having recurrent seizures and was diagnosed with epilepsy and was started on antiepileptic drugs. CT brain was done which showed brain atrophy. EEG could not be done properly due to unnecessary head movements.

During her routine hospital visits she had her plasma proteins and amino acid levels done in 2019 which showed elevated methionine levels (899 μmol/L normal range: 3-43 μmol/L) and slightly elevated ornithine levels (143 μmol/L normal range: 20-136 μmol/L). While all other tests including homocysteine levels, plasma lactate levels, ceruloplasmin levels, urine organic acids were normal.

Liver functions came to normal range in 2019 and jaundice episodes settled down but occasional episodes of respiratory tract infections with flu, fever, cough and chest congestion; and gastric infections with diarrhea and vomiting continued.

She had her first visit with Dr. Huma Arshad Cheema (HOD gastroenterology and hepatology Children Hospital and institute of child health, Lahore) in February 2020 at 4.5 years of age. It was the first time when she was advised genetic testing of herself and both parents, it was done and she was diagnosed with *hypermethionemia due to adenosine kinase deficiency* at 5 years of age. Both the parents are heterozygous carriers for the disease. She was advised on methionine free and protein deficient diet and was also started on methionine free milk formula but she could not digest the methionine free milk and it caused vomiting and diarrhea after every feed, however proteins were cut off from her routine diet. It improved her liver function tests and jaundice episodes settled but there was no improvement in her milestone achievement.

Until at 9 years of age she was wheelchair bound, and had developmental delay and marked hypotonia. She mostly needed support to sit, tried to hold and reach for objects, wore diapers, recognized familiar faces, and got anxious with strangers. Her gross motor age was of 9 months, fine motor of 12 months, speech of 6 months, and cognitive and social age of 9 months old baby.

Her weight was 15.5 kg and height was 106.6cm, features were still dysmorphic and had mild squint, In last one month she was having recurrent diarrhea episodes and was being investigated, latest reports showed her fecal calprotectin levels to be raised which indicated inflammatory bowel, before starting the treatment she developed massive ascites and jaundice, her oral intake was reduced and she had severe nausea and vomiting. She was hospitalized for IV fluid management and medication including albumin, steroids and antibiotics, bilirubin and GGT were markedly raised, with decreased HB, Platelets and WBCs. Coagulation profile was also disturbed with raised PT and INR. She was labelled as a case of decompensated liver disease secondary to ADK deficiency.

She showed very little improvement and was shifted to ICU when jaundice became very severe after 1 week of starting of treatment. She was transfused 1 pint of blood and 2 FFPs. She was in ICU care for last 10 days of her life and was on NG feed, she was vitally stable but clinically drowsy with decreased GCS and marked jaundice.

On detailed examination she was pale, jaundiced, and weak, lying in bed drowsy and irritated. Normal heart sounds but raised JVP, normal vesicular breathing bilaterally. There was tenderness and rebound tenderness positive in right hypochondrium. External genetalia were normal and still had mild dysplasia of both hip joints. Her epilepsy remained controlled with maximum dose of antiepileptic drugs throughout admission. She had frontal bossing, high forehead and deep-seated eyes and thin sparse hair.

She was in the category of Child-Pugh C (score 12) and her MELD score was 27. Interpretation of these scores was done with help of following tables.

MODEL FOR END STAGE LIVER DISEASE (MELD) SCORE ORIGINAL	
MELD= (0.957*ln(Serum creatinine) + 0.378*ln(Serum bilirubin) + 1.120*ln(INR) + 0.643)*10	
(If on hemodialysis, value for creatinine is automatically set to 4.0)	
Note: If any score is <1, MELD assumes the score is equal to 1.	
3 MONTH MORTALITY BASED ON MELD SCORES	
MELD SCORE	MORTALITY PROBABILITY
40	71.3% mortality
30-39	52.6% mortality
20-29	19.6% mortality
10-19	6.0% mortality
9 or less	1.9% mortality

Fig 3: Model for end stage liver disease (meld) score and mortality probability

Clinical and lab criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (Diuretic refractory)
Bilirubin (mg/dl)	<2	2-3	>3
Albumin(g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
INR	<1.7	1.7-2.3s	>2.3
	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1 year survival	100%	80%	45%

Fig 4: Child pugh score and interpretation

Record of the treatment in ICU and fresh lab reports is tabulated below:

Treatment started with IV meropenem, injection albumin, injection vitamin K, injection furosemide and infusion of normal saline along with tablet rifaximin and syrup benzoate through her NG. Her symptoms continued to progress with all the treatment, and she ended up with grade 3 hepatic encephalopathy with marked metabolic plus respiratory alkalosis (ph. 7.66), developed multiple bruises over her body, bleeding from her gums and through her NG, her feed was stopped, and she was treated palliatively. Parents and family were counselled about her terminal condition, eventually her urine output became nil, and she developed hepatorenal syndrome and after 10 days of ICU care she passed away On 15th June, 2024. due to multiorgan failure and respiratory arrest.

TABLE 1: Clinical presentation and lab reports of 10 days in icu care

	Clinical presentation	Serum ammonia levels and albumin	Renal function tests	Liver function tests and bilirubin	Complete blood picture	Coagulation profile	Serum electrolytes
Admission day (30 may)	Pale and jaundiced, well oriented, sick looking with gross ascites and spider veins visible	Ammonia:132 albumin: 3.0	Urea: 10 Creatinine: 0.5	ALT: 36 AST: 71 ALP: 298 Total bilirubin 2.2	Hb: 7.5 Wbc: 3.6 Platelet: 127	PT: 23 seconds INR: 2.6	
Day 3	Pale, jaundice increased, drowsy, sick looking with ascites improved		Urea:5.1 Creatinine: 63	Bilirubin: 11.2			Sodium: 146 Potassium: 4.2 Chloride: 104

Day 6	Jaundice increased, drowsiness increased, irritable, ascites	Albumin: 3.9	Urea: 4.4 Creatinine: 93		Hb: 10.8 (after 1 pint Blood) Wbc: 5.28 Platelet: 106		Sodium: 136 Potassium: 4.4 Chloride: 10
Day 9	Severely irritated (grade 3 encephalopathy) Gross ascites, sick looking, gasping			Bilirubin: 29 ALT: 150 AST: 150 ALP: 132 GGT:121		PT: 19.2 INR: 1.8 (after two FFPs transfused)	
Day 10				Bilirubin: 39 ALT: 131 AST: 148 ALP:116 GGT:99		PT: 21.3 INR: 2.01 APTT: 55	

DISCUSSION

Hypermethioninemia can occur with other metabolic disorders like homocystinuria and galactosemia but can also occur primarily without any association due to mutations in *MAT1A, GNMT* or *AHCY* gene.[6,1] These gives instructions to make enzymes which than are responsible for one of the multiple steps in methionine breakdown (Fig 1 and 2).

MAT1A produces methionine adenosyl transferase, *GNMT* makes N-methyltransferase and *AHCY* makes S-adenosylhomocysteine hydrolase which are used in methionine breakdown cycle hence mutation in any of the genes would lead to hypermethioninemia and produce similar symptoms.[7,8]

Previously less than 30 cases of adenosine kinase deficiency have been reported in literature none of which was from Pakistan. Phenotypically all the patients had same dysmorphic features. Almost 50% patients had macrocephaly; all was developmentally delayed with hypotonia.

ADK gene is present on chromosome 10q22, previous research report missense, nonsense and frameshift mutations, missense being the commonest.

Our case is ADK variant c.66-1G>T which disrupts the acceptor splice site.

In addition to this mutation genetic testing shows additional mutations in two other genes, in frame mutation in CFTR gene (heterozygous) and missense mutation in CYP17A1 gene (heterozygous) which are responsible for causing cystic fibrosis and congenital adrenal hyperplasia in patients who inherit the gene from both parents (homozygous pattern).

Consent: Informed written consent was taken from both the parents. We are thankful that they helped in every way to make this study possible.

Conflict of interest: None

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