Adenosine Kinase Deficiency
A Case Report

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INTRODUCTION: Adenosine kinase deficiency is an autosomal recessively inherited, rare disorder of methionine and adenosine metabolism. ADK gene mutations lead to heterogeneous clinical findings of dysmorphism, muscular hypotonia, epilepsy, and psychomotor retardation. Laboratory evaluation reveals elevated levels of liver enzymes, hyperbilirubinemia, hypermethioninemia and high plasma AdoHcy and AdoMet levels. Neuroradiological abnormalities include cerebral atrophy, hydrocephalus, nonspecific white matter changes, and delayed myelination. The diagnosis is confirmed by molecular analysis of the ADK gene. Here, we report this rare case with a novel pathogenic variant on ADK gene.

CASE REPORT: A 14-year-old male patient was consulted to the pediatric metabolism department with unexplained multisystemic involvement of neurological, hepatic and hematological findings. Medical history revealed when he was 4 years old, he had an acute hepatic insufficiency accompanied with hypotonia and psychomotor retardation without any specific etiology. He had elevated liver function tests, bilirubin and α-feto protein levels. Liver biopsy was compatible with portal fibrosis, bridging necrosis, mononuclear inflammatory infiltration in portal area with foci of piecemeal necrosis and regeneration nodules. He had multiple seizures when he was 5 years old and therefore on antiepileptic treatment. His parents were first degree cousins and had 2 healthy siblings. The mother had 2 spontaneous abortions. On physical examination, he had growth retardation, facial dysmorphism, axial hypotonia and peripheral spasticity. The liver is 4 cm palpable in the midcostal line below the costal margin. Echocardiography detected secundum atrial septal defect. Cerebral magnetic resonance imaging showed subcortical cerebral atrophy. Laboratory evaluation revealed macrocytic anemia and slightly elevated plasma homocysteine with normal B12 and folic acid levels. Plasma quantitative amino acid analysis detected elevated levels of methionine, alanine, tyrosine and phenylalanine which was attributed to chronic liver dysfunction. A cobalamin metabolism defect could not be excluded. Analysis of MMACHC gene for cobalamin C defect resulted normal. So, this confusing chronic clinical picture which was not solved with standard diagnostic methods led us to perform whole exome sequencing (WES). WES detected a novel, homozygous c.474delC (p.N159Ifs*18) pathogenic variant on ADK gene. In silico predictive tools classified this novel variant as highly pathogenic as it leads to a frameshift mutation and a premature stop codon. Both parents were heterozygous carriers of this mutation. The patient is currently 17-year-old, severely disabled and has fluctuating liver function tests.

CONCLUSION: The typical features of ADK deficiency is facial dysmorphism, cardiac malformations, liver involvement, and psychomotor retardation. Although our patient has all these prominent clinical manifestations, the overlapping findings led us to think more frequently seen inherited disorders at first. We would like to report this interesting and rare case to emphasize adding ADK deficiency in differential diagnosis of combined neurological, hepatic and cardiac involvement. Surprisingly our patient had megaloblastic anemia which was not previously reported in the literature. Also with this case we add a novel mutation in ADK deficiency.