
بسم الله الرحمن الرحيم

CEREBRAL CREATINE DEFICIENCY SYNDROME

HOSSEIN MORAVEJ, MD

PEDIATRIC ENDOCRINOLOGY AND METABOLISM

SHIRAZ UNIVERSITY OF MEDICAL SCIENCES

CLASSIFICATION OF IEM

- Treatable/untreatable
- Toxicity/ Enregy / Large molecules

CLASSIFICATION OF IEM

- Beneficial for patient/ Beneficial for parents/ harmful for patients and parents
- Association of CCDS and autism

- Beneficial for the patient:
- Biotinidase deficiency, Carnitine uptake defect, Classic PKU, Cerebral Creatine Deficiency
- Beneficial for the parents:
- 1st child
- Harmful?!!!
- Unnecessary diet, unnecessary expensive drugs, psychologic complications

CASE 1

- 05.05.98:
- A 3.2 y.o boy referred from a ped. Neurologist with the result of aa genetic test
- Physical exam:
- Wt: 12.2 kg, Lt: ?, HC: 48.8
- No neck holding, axial hypotonia but normal tone of extremities, no standing, no talking
- Epilepsy controlled with Na valproate

CASE 1

- EMG & NCV: normal
- Brin MRI: normal
- Whole Exome Sequencing: Cerebral Creatine Deficiency type 2

CASE 1

- Panel of creatine:
- Guanidinoacetate and creatine in serum and urine
- High guanidinocetate, low cretine

- Diagnosis:
- Guanidinoacetate Methyltransferaase deficiency

CASE 1

- Treatment:
- Creatine monohydrate, 200 mg/kg/d

CASE 1

- We gradually increased the dose and added Na. Benzoate
- 9 months later, at the ge of 4 y: Patient started walking
- 4.5 y.o: normal movement, but hyperactive, cognition was not good, Speech was better,
- 5.3 y.o: Cognition and speech was improving, hyperactivity was decreased.

ASSOCIATION OF CCDS AND AUTISM

A multicenter collaboration:

Isfahan, Tehran, Rasht, Ahwaz and Shiraz

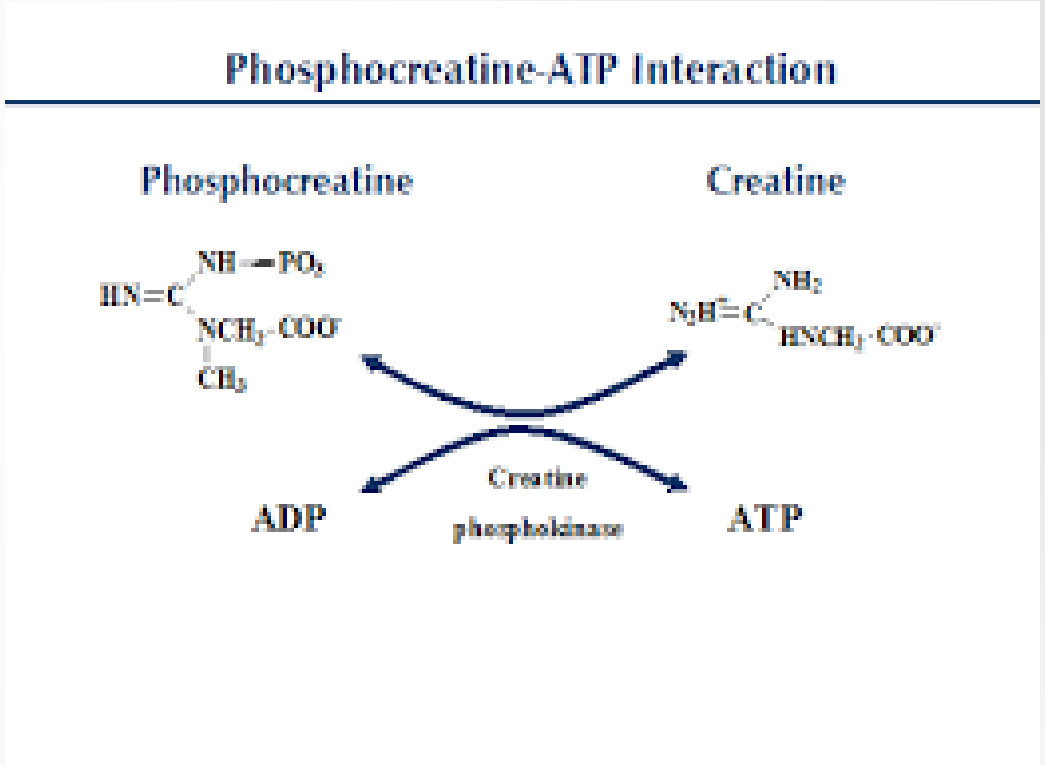
High association

- **Creatine**

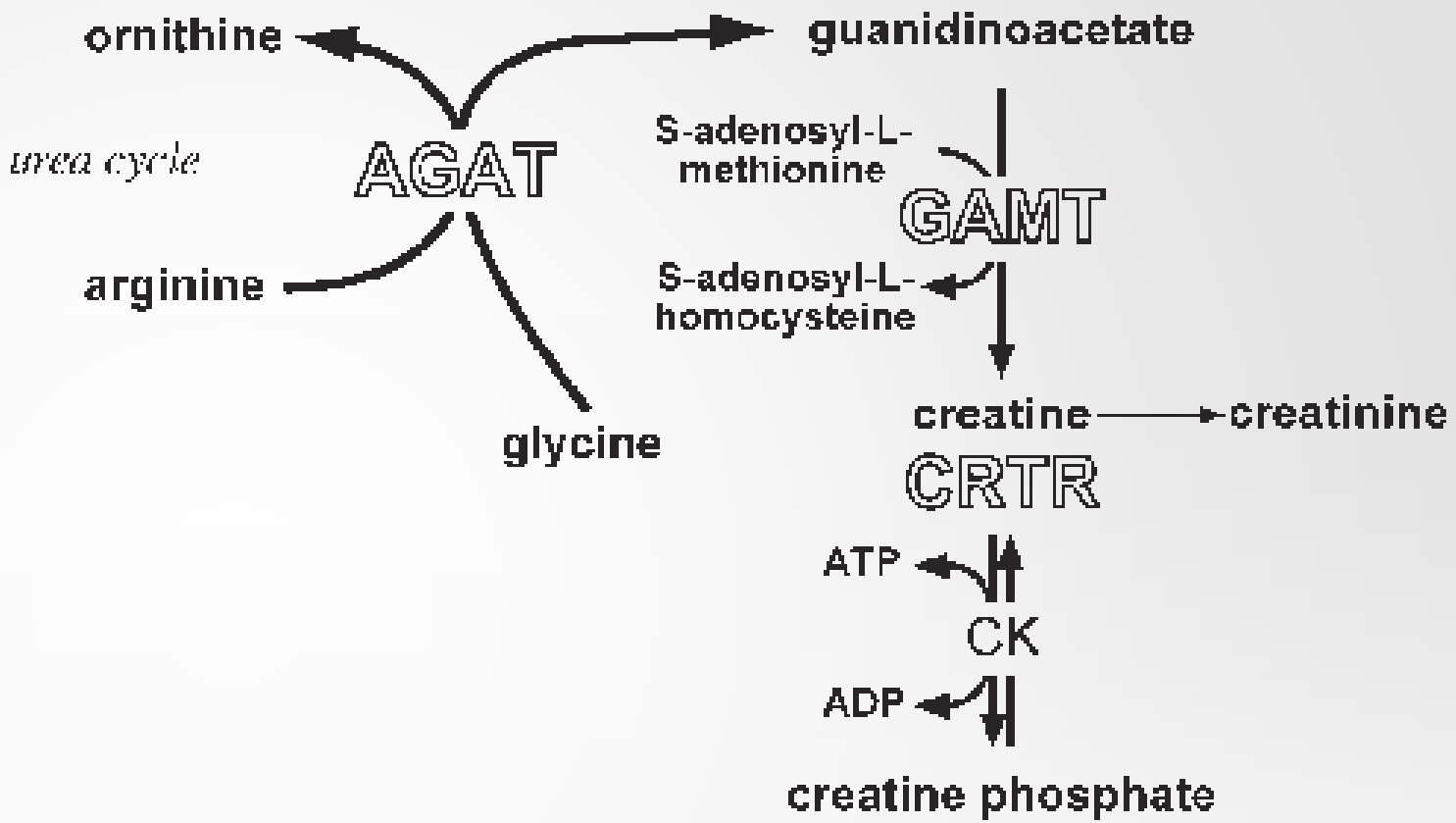
CREATINE

- A nitrogenous organic acid that is produced primarily in the kidney and liver
- Stored in tissues with high energy demands, such as skeletal muscle and the brain.

Its phosphorylated form (creatine-phosphate or phosphocreatine) is involved in the formation of adenosine triphosphate (ATP).



Creatin synthesis and metabolism



- **Cerebral Creatine Deficiency Syndrome (CCDS)**

CCDS

- Three identified types:
- Arginine : glycine amidinotransferase (AGAT) deficiency, AR
- Guanidinoacetate methyltransferase (GAMT) deficiency, AR
- Creatine transporter (CRTR) deficiency, a defect in the transport of creatine into the brain and muscle, X-linked

CLINICAL MANIFESTATIONS

- Intellectual disability, range from mild to severe.
- Behavioral problems
- Autism
- Speech delay
- Epilepsy
- Movement disorders
- Additional features: myopathy, muscular hypotrophy

CLINICAL MANIFESTATIONS

Another disorder affecting AGAT, but without (cerebral) creatine deficiency:

- Intramitochondrial aggregates that cause Fanconi syndrome and kidney failure.

Point:

- Patients with intellectual disability associated with autistic behaviors should be screened for congenital disorders of creatine synthesis and transport

DIAGNOSIS OF CCDS

- Measurement of the creatine signal in the brain by proton magnetic resonance spectroscopy (MRS)
- Measurement of Guanidinoacetate, creatine, and creatinine in the urine, plasma, and/or cerebrospinal fluid (CSF) .
- Measurement of levels in the urine only is generally sufficient. However, MRS is more sensitive and specific and, therefore, is usually performed as a confirmatory test.

DIFFERENTIAL DIAGNOSIS

- Disorders associated with secondary deficiency of cerebral creatine: Argininosuccinic aciduria (argininosuccinate lyase deficiency),
- Citrullinemia type I (argininosuccinate synthetase deficiency)
- Gyrate atrophy of the choroid and retina (due to ornithine aminotransferase deficiency).
- These patients have partial cerebral creatine deficiency identified by MRS, but a normal urine creatine-to-creatinine ratio, and unremarkable or nonspecific changes of GAA concentrations in body fluids.

TREATMENT

- Oral supplementation of high-dose creatine-monohydrate for all three congenital creatine deficiency disorders
- GAA-reducing strategies (high-dose ornithine, arginine-restricted diet) as an additional treatment for GAMT deficiency
- Supplementation of substrates for intracerebral creatine synthesis (eg, arginine, glycine) to treat CRTR deficiency

TREATMENT

- GAMT deficiency:

  Early diagnosis and treatment can result in normal development .

- AGAT deficiency: Similar to GAMT
- CRTR deficiency: Treatment has been less successful.

TAKE HOME MESSAGES

- لطفا در بیماران دچار اختلال ذهنی، بویژه تاخیر تکلم، اختلال متابولیسم کراتین را در نظر داشته باشید.
- در این گونه موارد، سطح کراتین، کراتینین و گوانیدینواستات را چک کنید.


THANK YOU
FOR YOUR
ATTENTION