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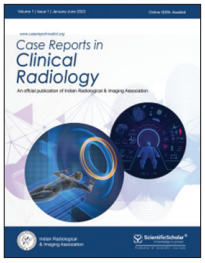

Case Report

Magnetic resonance spectroscopy as a diagnostic tool in cerebral creatine deficiency syndrome 3

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Received: 01 August 2024
Accepted: 11 November 2024
EPub Ahead of Print: 12 December 2024
Published:

DOI
10.25259/CRCR_92_2024

Quick Response Code:

ABSTRACT

Cerebral creatine deficiency syndrome-3 is a rare autosomal recessive disorder characterized by disturbance of expressive and cognitive speech, developmental delay, intellectual deficiency and myopathy. In some rare cases, it is associated with behavioral issues and seizures which usually have an early onset. A 44-month-old girl presented with complaints of speech delay, psychomotor regression, and features of proximal myopathy. Contrast-enhanced magnetic resonance imaging brain was essentially normal. Multivoxel magnetic resonance spectroscopy (MRS) demonstrated absence of definable creatine peak at 3.0 ppm. Follow-up MRS, post-creatine monohydrate supplementation revealed appearance of creatine metabolite peak at 3.0 ppm suggesting treatment response. In this case report, we are highlighting the potential of MRS as a reliable method of detecting cerebral creatine levels in the cerebral creatine deficiency syndrome as well as documentation of treatment response with oral creatine.

Keywords: Magnetic resonance spectroscopy, Cerebral creatine deficiency syndrome, Speech delay

INTRODUCTION

The creatine-phosphocreatine system is vital for energy metabolism.[1] It enables rapid adenosine triphosphate (ATP) generation/regeneration by transferring high-energy phosphate groups from phosphocreatine to adenosine diphosphate (ADP) during periods of high energy demand, sustaining the cellular function.[1]

Cerebral creatine deficiency syndrome (CCDS) 3 is a rare autosomal recessive disorder. It occurs due to homozygous mutation in the glycine amidinotransferase (GATM) gene on chromosome 15q21.[2] This leads to arginine glycine amidinotransferase (AGAT) deficiency impairing the endogenous cerebral synthesis of creatine impacting the brain myelination as well as bioenergetics.[3] The estimated carrier frequency of AGAT deficiency was one in 1292 in the general population using the exome aggregation consortium (ExAC) browser beta database.[4] If left untreated, children with CCDS 3 can present with disturbance of expressive and cognitive speech, severe developmental delay, intellectual deficiency, and myopathy presenting as proximal muscle weakness and atrophy later in life.[5] Rarely, it may be associated with behavioral issues and seizures, which are more commonly seen in CCDS-1 and CCDS-2.[2] However, early diagnosis and treatment may prevent the phenotypic expression of the disease.[6,7] Total creatine (tCr) constitutes one of the most prominent signals in human brain magnetic resonance (MR) spectra due to its high energy demand. A notable reduction in the tCr signal suggests a serious impairment in creatine metabolism.[8] Therefore, suspected patients should promptly undergo MR imaging

(MRI) with spectroscopy. Absence of definable creatine peak at 3.0 ppm and/or biochemical and genetic correlates helps in the early diagnosis and treatment of the condition.

CASE REPORT

A 44-month-old girl, born out of a consanguineous marriage, with no significant perinatal history, presented with speech delay and psychomotor regression. The child had progressive proximal muscles weakness with decreased muscle mass. No complaints of seizures or behavioral issues were noted. In addition, a paternal uncle of the child had similar history which was falsely diagnosed as autism for speech disorder and the cause of myopathy was left undiagnosed.

On examination, there was poor muscle mass with hypotonia in the proximal muscles. Positive Gower's sign was noted. Deep tendon reflexes were preserved.

Contrast-enhanced MRI brain with conventional MRI brain sequences was done on Siemens MAGNETOM Aera 1.5T MRI machine. MRI consisted of hospital examination protocol including turbo spin echo T1- and T2-weighted sequences with transversal slice thickness of 5 mm, sagittal T1 and coronal T2 slices of 4 mm. MRI brain was essentially normal. Multivoxel MR spectroscopy (MRS) was done at long time to echo (TE) (135 ms) and short TE (30 ms). Voxels were placed in white matter and gray matter. MRS did not demonstrate a definable creatine peak at 3.0 ppm [Figure 1]. N-acetylaspartate (NAA) and choline metabolite peaks were normal. In the given clinical settings, these findings were consistent with CCDS. Biochemical and genetic correlation was suggested.

Laboratory studies yielded increased serum creatine kinase (CK). Whole exome sequencing revealed homozygous pathogenic mutation in GATM gene on chromosome 15 confirming the diagnosis of CCDS type 3 [Figure 2]. Genome sequencing of both the parents revealed heterozygous mutation in GATM gene on chromosome 15 [Figure 3].

The patient was started on creatine monohydrate supplementation to replenish cerebral creatine levels. Interval MRS done 5 months post-treatment revealed appearance of the creatine metabolite peak at 3.0 ppm, suggesting treatment response [Figure 1].

DISCUSSION

The creatine-phosphocreatine system enables rapid ATP generation/regeneration by transferring high-energy phosphate groups from phosphocreatine to ADP during periods of high energy demand, sustaining the cellular function.[1] Roughly, half of our daily creatine comes from dietary sources, while the remaining half is synthesized internally.

This synthesis begins with glycine and arginine converting into guanidinoacetate through arginine amidinotransferase (AGAT). This is followed by guanidinoacetate transforming into creatine through guanidinoacetate methyltransferase (GAMT).[1] Cells utilize creatine by converting it into phosphocreatine for internal energy use or transporting it to other cells through the creatine transporter [Figure 4].

CCDSs are group of rare, inborn errors of creatine metabolism which impair the formation, transport or utilization of creatine. There are three main types of CCDS: Creatine transporter deficiency (CTD), GAMT deficiency, and AGAT deficiency [Figure 4].[1,2]

AGAT deficiency is one of the three inborn errors of creatine metabolism caused due to GATM gene mutation impairing the endogenous cerebral creatine synthesis.[2] Creatine serves as a sensor for cell methylation and energy levels, influences key neurotransmissions in the central nervous system (CNS) [GABAergic (Gamma-Aminobutyric Acid) and glutamatergic], and supports the creatine-creatine phosphate cycle. Creatine also functions as an energy source and antioxidant, protecting against energy depletion and oxidative stress in brain as well as muscles.[9]

Various studies have found an increase in postnatal expression of enzymes involved in creatine synthesis, coinciding with active CNS myelination.[10] It was found that oligodendrocytes are the primary producers of internally synthesized creatine in the adult CNS.[3] Disruption of this endogenous creatine synthesis can influence the timing of myelination and potentially affect brain energy metabolism.[3]

MRI forms the primary imaging modality of choice in developmental disorders of brain. MRS holds special relevance in metabolic and molecular disorders of the CNS. It analyzes hydrogen signals from molecules other than water. It produces spectra that plot peak amplitudes (Y-axis) against specific frequencies (X-axis), revealing hydrogen nuclei in different chemical environments.[11,12] Each metabolite is distinguished by unique resonance frequencies and characteristic shapes, widths, and heights of its peaks. At commonly used field, strengths such as 1.5 or 3.0 Tesla, signals from choline, creatine, and NAA are typically observed in the normal brain when using long echo times (e.g., 140 or 280 ms). However, in pathological conditions where their concentrations are elevated, compounds such as lactate and alanine may also become detectable. Conversely, with short echo times (e.g., 35 ms or less), additional compounds, such as glutamate, glutamine, myo-inositol, as well as lipids and macromolecular resonances, can be detected.

The "creatine" methyl resonance ("Cr," 3.03 ppm) is a composite peak consisting of both creatine and phosphocreatine, compounds involved in energy

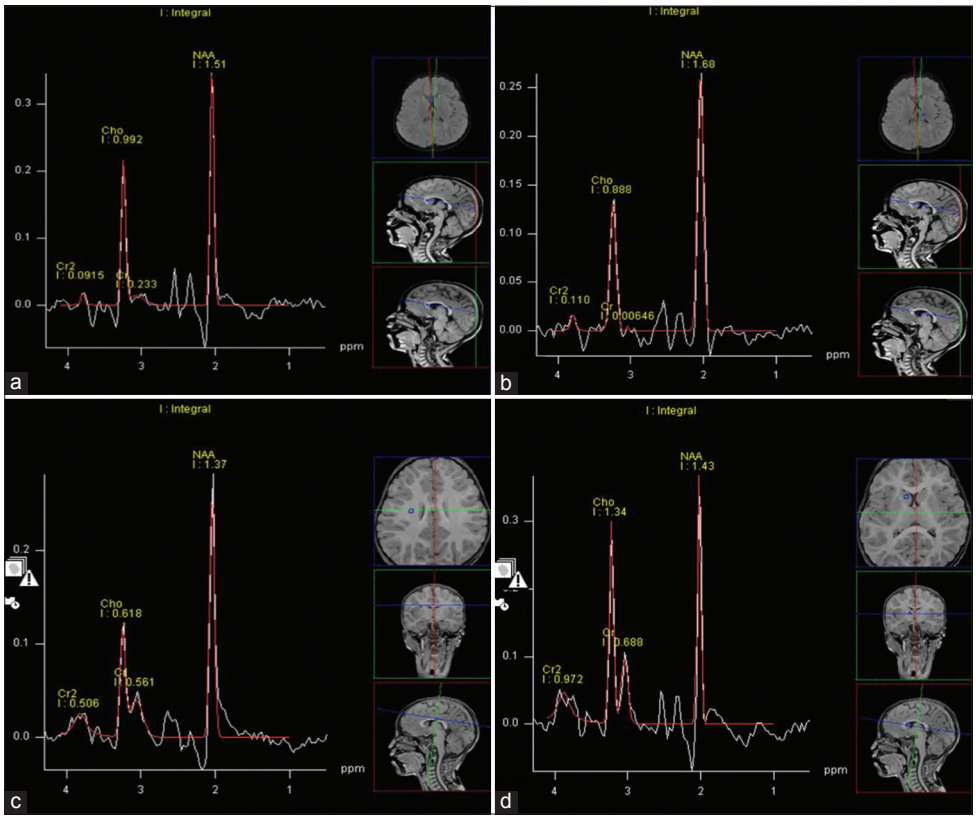

Figure 1: A 44-month-old girl, born out of consanguineous marriage, with no significant perinatal history, presented with speech delay and psychomotor regression. Magnetic resonance spectroscopy images showing absence of demonstrable creatine peak at 3 ppm when voxels were placed in (a) white matter and (b) gray matter. She was started on creatine supplementation after diagnosis of cerebral creatine deficiency syndrome 3. Interval magnetic resonance spectroscopy done 5 months post-treatment revealed appearance of creatine peak at 3 ppm when voxels were placed in (c) white matter and (d) gray matter.

Gene & Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classifcation
GATM NM_001482.3	c.76C>T p.Arg26*	Exon 2	Homozygote	CADD: 35 SIFT: Tolerated Polyphen2: N/A MT: Damaging	CEREBRAL CREATINE DEFICIENCY SYNDROME 3; CCDS3:612718	Autosomal Recessive	Likely Pathogenic

Figure 2: A 44-month-old girl, born out of consanguineous marriage, with no significant perinatal history, presented with speech delay and psychomotor regression. Whole exome sequencing revealed pathogenic mutation in glycine amidinotransferase gene on chromosome 15 confirming the diagnosis of cerebral creatine deficiency syndrome type 3. *Genomic position on assembly GRCh37, (G: Guanine, C: Cytosine). **Number of applied *in silico* programs predicting the effect of the variant on the protein outcome. CADD: Combined annotation dependent depletion [v1.6], SIFT: Polyphen-2, MT: Mutation taster, N/A: Not applicable, OMIM: Online Mendelian Inheritance in Man.

metabolism. There is significant regional variation seen in creatine distribution, with higher levels seen in gray matter compared to white matter. A significant decrease in the "Cr" signal using long echo times indicates a severe disorder of creatine metabolism.[8] It may be associated with thinning of corpus callosum, abnormalities in white matter, extracerebral space enlargement, and cerebral atrophy.[13] However, absence of morphological abnormalities does not exclude CCDS. MRS is the definitive imaging modality for diagnosis.

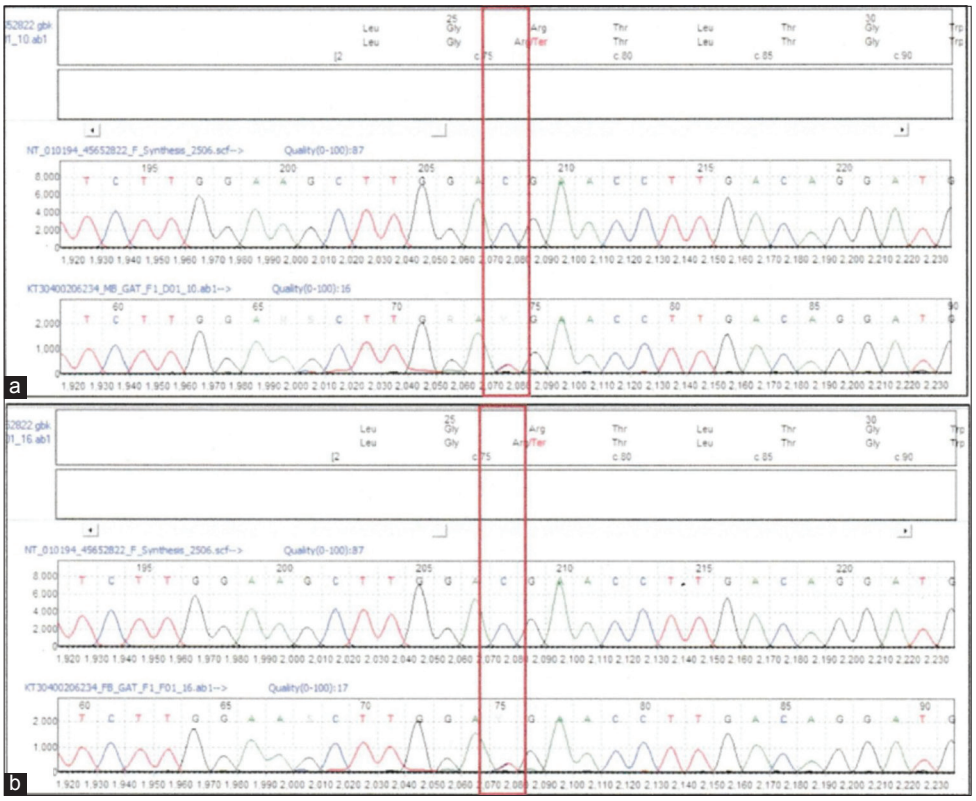

Figure 3: A 44-month-old girl, born out of consanguineous marriage, with no significant perinatal history, presented with speech delay and psychomotor regression. Sanger sequencing data (electropherogram) of the patient's both parents was performed for confirmation of variant in Glycine amidinotransferase (GATM) gene. (a and b) Showing nucleotide change at Chr15:c.76C>T, (C: Cytosine, T: Thymine) (p.Arg26*) in GATM gene in heterozygous state, suggestive of autosomal recessive inheritance.

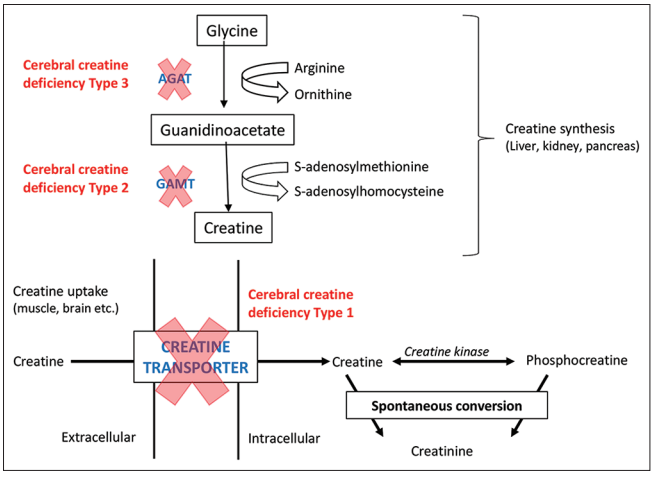

Figure 4: Creatine metabolic pathway, including biosynthesis, cellular uptake, phosphotransfer and conversion to creatinine, along with associated inborn errors of metabolism. AGAT: Arginine Glycine amidinotransferase; GAMT: Guanidinoacetate methyltransferase

CONCLUSION

MRS stands out as one of the most sensitive and specific non-invasive diagnostic tool in CCDS. Most of the patients presenting with speech delay with or without psychomotor regression are falsely diagnosed as autism spectrum disorders or go undiagnosed due to poor clinical know-how. Hence, every suspected case of developmental delay with speech disorder must undergo MRI with MRS as normal MRI does not exclude creatine deficiency disorder.

TEACHING POINTS

1. MRS stands out as one of the most sensitive and specific non-invasive diagnostic tool in CCDS.
2. Most of the patients presenting with speech delay, with or without psychomotor regression are falsely diagnosed as autism spectrum disorders or go undiagnosed due to poor clinical know-how.
3. Every suspected case of developmental delay with speech

disorder must undergo MRI with MRS as normal MRI does not exclude creatine deficiency disorder.

MCQs

1. CCDS type 3 is caused due to defect in?
   a. CTD
   b. GAMT deficiency
   c. AGAT deficiency
   d. CK

Answer Key: c

2. What is the mode of inheritance of CCDS 3?
   a. Autosomal recessive
   b. Autosomal dominant
   c. X linked recessive
   d. X linked dominant

Answer Key: a

3. Which of the following is seen in CCDS3 on MRS?
   a. Elevated creatine
   b. Elevated NAA
   c. Reduced/absent creatine
   d. Reduced/absent NAA

Answer Key: c

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Garg A, Gupta R, Modi JAK, Kabiraj D. Magnetic resonance spectroscopy as a diagnostic tool in cerebral creatine deficiency syndrome 3. Case Rep Clin Radiol. doi: 10.25259/CRCR_92_2024