Long-term follow-up and treatment in nine boys with X-linked creatine transporter defect

Jiddeke M. van de Kamp · Petra J. W. Pouwels · Femke K. Aarsen · Leontine W. ten Hoopen · Dirk L. Knol · Johannes B. de Klerk · Ireneus F. de Coo · Jan G. M. Huijmans · Cornelis Jakobs · Marjo S. van der Knaap · Gajja S. Salomons · Grazia M. S. Mancini

Received: 3 February 2011 / Revised: 5 April 2011 / Accepted: 19 April 2011 / Published online: 10 May 2011
© The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract The creatine transporter (CRTR) defect is a recently discovered cause of X-linked intellectual disability for which treatment options have been explored. Creatine monotherapy has not proved effective, and the effect of treatment with L-arginine is still controversial. Nine boys between 8 months and 10 years old with molecularly confirmed CRTR defect were followed with repeated 1H-MRS and neuropsychological assessments during 4–6 years of combination treatment with creatine monohydrate, L-arginine, and glycine. Treatment did not lead to a significant increase in cerebral creatine content as observed with H1-MRS. After an initial improvement in locomotor and personal-social IQ subscales, no lasting clinical improvement was recorded. Additionally, we noticed an age-related decline in IQ subscales in boys affected with the CRTR defect.

Introduction

Creatine is important for the energy homeostasis in the central nervous system (CNS) (Wyss and Kaddurah-Daouk 2000) and might act as a neuromodulator (Almeida et al. 2006). Creatine is both taken up from the diet and...
synthesized endogenously, mainly in the kidney, pancreas, and liver. In the first step of the biosynthesis, catalyzed by arginine/glycine amidotransferase (AGAT), guanidinoacetic acid and ornithine are formed from arginine and glycine. In the second step, catalyzed by guanidinoacetate methyltransferase (GAMT), guanidinoacetic acid is methylated into creatine. Creatine is then transported through the blood to creatine-requiring organs, mainly the brain and muscles, where it is taken up via the creatine transporter (CRTR) (Wyss and Kaddurah-Daouk 2000).

Cerebral creatine deficiency, which can be diagnosed by in vivo proton magnetic resonance (\(^1\)H-MRS) of the brain, causes neurological symptoms. The deficiency can be caused by autosomal recessive biosynthesis defects (AGAT or GAMT deficiency) or X-linked CRTR defect. The first male patient with CRTR defect was described in 2001 (Cecil et al. 2001; Salomons et al. 2001). Patients present with intellectual disability (ID), severe speech delay, behavior disturbances, and epilepsy (Stöckler and Salomons 2006).

In AGAT and GAMT deficiency, creatine supplementation has led to a partial restoration of the cerebral creatine content and attenuation of the symptoms (Mercimek-Mahmutoglu and Stockler-Ipsirolu 2009). In CRTR defect, high plasma creatine levels might result in some cellular creatine uptake via alternative mechanisms or residual activity of CRTR. CRTR-deficient fibroblasts take up creatine when incubated in high creatine concentrations (DeGrauw et al. 2002). However creatine monotherapy has not proved to be successful in patients with CRTR defect (Anselm et al. 2006, 2008; Bizzi et al. 2002; DeGrauw et al. 2002; Dezortova et al. 2008; Poo-Arguelles et al. 2006).

Brain cells appear to be capable of endogenous creatine synthesis since AGAT and GAMT are expressed in all brain cells (Braissant et al. 2001) and synthesis has been observed in brain cell cultures (Dringen et al. 1998). Provision of arginine increased guanidinoacetic acid (GAA) and creatine synthesis in astroglial cells (Dringen et al. 1998), the rat kidney (Edison et al. 2007) and, in combination with glycine, in human CRTR-deficient lymphoblasts (Leuzzi et al. 2008). Supplementation with creatine precursors L-arginine and glycine might, therefore, increase endogenous cerebral creatine synthesis. Chilosi et al. observed improvement and an increase in cerebral creatine (although still well below normal) after 1-year supplementation with L-arginine in an 8.6-year-old male patient with CRTR defect (Chilosi et al. 2008). Treatment with creatine combined with arginine and glycine also resulted in resolution of severe seizures in a 9-year-old girl with CRTR defect (Mercimek-Mahmutoglu et al. 2010). However Fons et al. (2010) reported no effect of a 9 month L-arginine supplementation in four male patients. The effectiveness of L-arginine supplementation therefore remains controversial.

We describe the 4–6 year follow-up with repeated \(^1\)H-MRS and neuropsychological assessments during a pilot study in nine boys who were diagnosed in the Netherlands shortly after the discovery of the creatine transporter defect in 2001 and were treated with creatine monohydrate, L-arginine, and glycine supplementation.

Subjects and methods

Subjects

Between 2003 and 2005, nine boys (four sib pairs, including one twin, and one single case), between 8 months and 10 years old (mean 5.3 years; median 3.9 years) were diagnosed with CRTR defect based on elevated urinary creatine/creatinine ratio, cerebral creatine depletion on \(^1\)H-MRS, and mutation in the \(\text{SLC6A8}\) gene and were started on treatment with creatine monohydrate, L-arginine, and glycine. Clinical details of the patients are summarized in Table 1. Two sibpairs patients have been published before (Mancini et al. 2005).

Treatment

All patients were started between 2003 and 2005 on oral creatine monohydrate 400 mg/kg and oral L-arginine 400 mg/kg per day, divided into two to three doses. In the two youngest patients (patients 8 and 9), 150 mg/kg glycine per day was added from the start. In five other patients, glycine was added after 15–21 months. Two brothers (patients 1 and 2) were never started on glycine treatment due to family circumstances. The regimen was chosen on the basis of the creatine supplement used for GAMT deficiency and L-arginine for patients with urea cycle defects. The glycine dose was chosen in a 1:1 molar ratio with L-arginine. These dosages are known to lack side effects and to be palatable and well tolerated. The individual treatment protocols are depicted in Fig. 1. Treatment was discontinued in 2009–2010 because of lack of evident response. The study protocol was discussed and supported by the Metabolic Section of the Dutch Pediatric Society.

Follow-up

Neuropsychological assessment and measurement of cerebral creatine by \(^1\)H-MRS were performed before the start of treatment and one to three times during treatment. The treatment duration at the last neuropsychological assessment was 12–48 months (mean 33) and at the last \(^1\)H-MRS 20–31 months (mean 25) (Fig. 1). Evaluation further consisted of check-ups twice yearly (history and physical examination) and biochemical analysis of urinary and plasma creatine,
| Patient | Age at start | Creatine uptake (pmol/μg protein) | Brain tCr at start a ( % normal mean) | SLC6A8 mutation | Total IQ at start | Psychiatric assessment (DSM-IV Axis I) | Epilepsy and age of onset | Urine cr/crn ratio | Urine GAA b (mmol/mol creatinine) |
|---------|--------------|----------------------------------|------------------------------------|-----------------|-----------------|-----------------------------------|--------------------------|-----------------|-------------------|
|         |              |                                  |                                    |                 |                 | At start                    | During                    | At start | During | At start | During | At start | During |
| 1       | 10 years     | 3 months                         | 2.89                                | 28              | c.1631 C>T;     | ADHD, combined type;       | No (epileptic activity on EEG at 6 years) | 1.8     | 6.2    | 56      | 80     |
|         |              |                                  |                                    |                 | p.(Pro544Leu)   | some signs of PDD NOS;     |                          |                     |                   |                   |
|         |              |                                  |                                    |                 |                 | mixed receptive-expressive language disorder |                          |                     |                   |                   |
| 2       | 8 years      | 4 months                         | 3.16                                | 29              | c.1631 C>T;     | ADHD, combined type;       | No (epileptic activity on EEG at 4 years) | 1.5     | 5.6    | 58      | 98     |
|         |              |                                  |                                    |                 | p.(Pro544Leu)   | some features PDD NOS and ODD; mixed receptive-expressive language disorder |                          |                     |                   |                   |
| 3       | 8 years      |                                  | 1.47                                | 29              | c.1495+5 G>C    | ADHD, combined type        | No                        | 2.7     | 11.3   | 141     | 68     |
| 4       | 5 years      | 11 months                        | 1.21                                | 24              | c.1495+5 G>C    | Diagnosis deferred; some signs of ADHD and PDD NOS | No                        | No                   | nd     | 11.7   | 40      | 112    |
| 5       | 3 years      | 11 months                        | 0                                   | 23              | c.570_571del;   | PDD NOS; signs of ADHD     | No                        | 4.0     | 4.7    | 114     | 179    |
|         |              |                                  |                                    |                 | p.(Ala191Gln6X10) |                                   |                          |                     |                   |                   |
| 6       | 3 years      | 11 months                        | nd                                  | 25              | c.428_430del;   | PDD NOS; signs of ADHD     | 3 years 11 months         | Unchanged           | nd     | 15.3   | nd      | 139    |
|         |              |                                  |                                    |                 | p.(Tyr143del)   |                                   |                          |                     |                   |                   |
| 7       | 3 years      | 11 months                        | nd                                  | 22              | c.428 430del;   | PDD NOS; signs of ADHD     | No                        | 3.5     | 10.4   | 67      | 112    |
|         |              |                                  |                                    |                 | p.(Tyr143del)   |                                   |                          |                     |                   |                   |
| 8       | 3 years      | nd                               | 21                                  | 51              | c.92dc;        | Autistic disorder           | Possible insult at 1 year 7 months | 3.5     | 17.0   | 96      | 244    |
|         |              |                                  |                                    |                 | p.(Pro31ArgfsX66) |                                   |                          |                     |                   |                   |
| 9       | 8 months     | nd                               | 22                                  | 65              | c.92dc;        | nd                         | 8.3                        | 24.6    | 354    | 239    |
|         |              |                                  |                                    |                 | p.(Pro31ArgfsX66) |                                   |                          |                     |                   |                   |

**tCr** Total creatine, cr/crn creatine/creatinine, GAA guanidinoacetate, ADHD attention-deficit hyperactivity disorder, PDD NOS pervasive developmental disorder not otherwise specified, ODD oppositional defiant disorder, nd not determined

a Mean of means of four brain regions

b Mean values from several measurements

c Reference values from Almeida et al. (2004)
guanidinoacetate, and amino acids. A renal ultrasound was performed to screen for renal stone formation during the treatment. Eight of the nine boys were seen by a child psychiatrist to classify their behavioral problems (Table 1).

Methods

Neuropsychological function was assessed with the Griffiths Mental Developmental Scales (with locomotor, personal-social, hearing and speech, hand and eye coordination, and performance subscales). In patients 3 and 4, the Snijders-Oomen Non-Verbal Intelligence Test (SON-R 2 1/2-7) and the Denver Developmental Screening Test (DDST) were used instead of the Griffiths scales at the neuropsychological assessment before treatment.

$^1$H-MRS spectroscopy of the brain was performed at 1.5 T (Siemens Vision, Erlangen, Germany) using a standard CP head coil. Single-voxel STEAM spectroscopy [repetition time (TR)/echo time (TE)/mixing time (TM)= 6,000/20/10 ms; 64 acquisitions] was obtained from volumes-of-interest (VOIs) in parietal gray matter (10 ml), parietal white matter (5 ml), basal ganglia (5 ml), and cerebellar vermis (8 ml) (Pouwels et al. 1999). Spectra were quantified using LCModel as described previously (Pouwels et al. 1999; Provencher 1993). In the current study we focused on the concentration of total creatine (Cr) (sum of creatine and phosphocreatine), which was expressed in mmol/l VOI (mM).

GAA and creatine were measured in plasma and urine using stable isotope dilution gas chromatography-mass spectrometry according to Almeida et al. (2004).

The creatine uptake assay in cultured skin fibroblasts after incubation at 25 μM creatine and genomic sequence analysis of the SLC6A8 gene was performed as previously described (Rosenberg et al. 2007).

Fig. 1 Treatment protocol and timing of neuropsychological assessments and $^1$H-MRS in the individual patients. Double-hatched bars depict treatment with creatine and L-arginine. Hatched bars depict treatment with creatine, L-arginine, and glycine. Black rectangles depict neuropsychological assessments and gray rectangles $^1$H-MRS assessments

Statistical analysis

Statistical analysis was performed on the neuropsychological tests, $^1$H-MRS measurements, and growth parameters. To account for repeated measurements within subjects, data were analyzed using a linear mixed model in SPSS (v. 15.0). In longitudinal studies it is possible to separate cross-sectional and longitudinal age effects (e.g., Fitzmaurice et al. 2004). First a model with treatment, cross-sectional and longitudinal age effects was fitted. Since the cross-sectional and longitudinal effects were equal, a simpler model with treatment, region of measurement (only in analysis of $^1$H-MRS) and a common age effect was fitted, and results for the latter model are presented. Significance value was set at $P<0.05$.

Results

Adverse effects and compliance

In general, no adverse effects were reported. The parents of patients 3 and 4 reported that their sons’ hyperactive behavior increased after the addition of glycine to the treatment and decreased after the discontinuation of the creatine/arginine/glycine treatment. Renal ultrasounds (performed in eight boys) did not show calcifications or renal stones.

The urinary creatine/creatinine ratio (Table 1) increased during treatment and could be used to follow compliance of the creatine treatment. However in three patients (patients 1, 2, and 4) collection of urinary samples was sometimes difficult for the families. Little increase was seen in patient 5 and his parents reported problems administering the supplements. Increases in urinary GAA were found during treatment but not consistently (Table 1). No consistent changes were found in ornithine, L-arginine, and glycine levels in urine or plasma, making assessment of compliance with these supplements difficult. Therefore the results of the neuropsychological assessment and $^1$H-MRS in all patients were used for statistical evaluation irrespective of compliance.

Clinical assessment

Epileptic seizures occurred, with low seizure frequency, in five patients (Table 1). In four patients the onset was after the start of the supplementation treatment, although one patient probably had seizures before. Seizures were easily controlled by valproate monotherapy, as reported for untreated CRTR patients. Initially improved concentration, speech, and locomotion were reported in several patients. Height and weight increased more than two standard
deviation (SD) scores in two and three patients, respectively, and between one and two SD scores in an additional three and two patients, respectively, but decreased more than two SD scores in one other patient. Head circumference did not change more than one SD score in any of the patients. Statistical analysis of the whole group did not show any significant changes of the growth parameters with treatment.

Neuropsychological assessment

The developmental courses on the Griffiths subscales (Fig. 2) show in the whole group a decrease in scores for hearing and speech and for hand and eye coordination with time. Notably, some patients had an initial increase in scores on locomotor and personal-social subscales followed by a decrease. Statistical analysis (Table 2) confirmed a significant negative correlation between age and scores on the hearing and speech ($P=0.019$) and the hand and eye coordination ($P=0.017$) subscales, although there was also still a just significant negative effect ($P=0.043$) of treatment with creatine plus L-arginine and glycine. Statistical analysis also confirmed a significant treatment effect on locomotor ($P=0.004$) and personal-social ($P=0.008$) subscales during treatment with creatine combined with L-arginine alone. However after addition of glycine this effect was not significant anymore.

1H-MRS spectroscopy of the brain

Figure 3 shows the 1H-MRS spectra of one patient before and during treatment. The course of the Cr concentration during treatment in the four brain regions of all nine patients is shown in Figure 3. The dotted line represents the measurements before treatment, the solid line represents the measurements during treatment, and the numbers stand for the treatment conditions (0 before start, 1 during treatment with creatine and arginine, 2 during treatment with creatine, arginine, and glycine).
patients is shown in Fig. 4. There was no significant increase in Cr during treatment in any of the regions. The slight variation in Cr concentration can be entirely due to the reproducibility of the measurement. Based on the error estimate of the LCModel analysis and the actual low concentration of Cr, the obtained values will have a variability of at least 0.5 mM. Overall, Cr concentrations in cerebellum (mean 2.0±0.5 mM) and basal ganglia (2.0±0.5 mM) of the whole group were significantly higher than in cortex (1.5±0.3 mM) and white matter (1.5±0.4 mM) (P<0.05). There was no clearly detectable GAA signal in any of the patients’ spectra either before or during treatment. With LCModel a low concentration of GAA may be fitted, but this is a small value that is unreliable, comparable to the value in healthy controls.

### Table 2

| Grifiths scales | Age effect | Treatment vs no treatment | Treatment vs arg | Treatment vs arg+gly |
|-----------------|------------|---------------------------|-----------------|---------------------|
| Total           | −0.88 (−2.1; 0.3) | 0.164 | 0.049* | 0.190 |
| Locomotor       | −1.0 (−5.1; 3.2) | 0.028 | −0.041 | 0.086 |
| Hearing and speech | −1.6 (−7.3; 3.5) | 0.528 | 0.517 | 0.485 |
| Personal-social | 1.0 (3.6; 1.5) | 0.004* | 0.004 | 0.088 |
| Hand-eye coordination | 0.2 (−5.1; 5.5) | 0.050* | 0.066 | 0.317 |
| Performance     | −0.4 (−1.6; 2.4) | 0.646 | 0.646 | 0.646 |

*P<0.005

**Fig. 3** Gray matter 1H-MRS spectra of patient 4 at start of treatment at age 5 years 11 months and during treatment at age 8 years 8 months. Cr concentrations in this brain region are 1.5 and 1.7 mM, respectively.

### Discussion

During the 4-6 years of follow-up of nine boys with the CRTR defect, we did not find enough evidence to conclude that treatment with creatine monohydrate, L-arginine, and glycine effectively improves cerebral creatine and/or development, as assessed by neuropsychological tests and 1H-MRS.

 Nonetheless, subjective improvements were reported by parents and caretakers during the first months of treatment. Also formal neuropsychological testing did indeed show significant improvements in motor and social skills in the whole group during the first assessments, while most patients were still on creatine monohydrate plus L-arginine treatment without glycine. However this effect did not last. It is unlikely that this is caused by the addition of glycine because scores also decreased in patients who were not (yet) started on glycine. Scores on the hearing and speech and the hand-eye coordination subscales even declined during treatment. Probably this is mainly age-related and not due to treatment because older patients
already had lower scores at the start of treatment. Statistical analysis confirmed a significant negative correlation with age. An age-related decline in IQ scores is also known to occur in Down’s syndrome and fragile X syndrome (Fisch et al. 2007) and might be common to more mental retardation disorders. This does not necessarily mean that these conditions are progressive. When the rate of development slows down and reaches an early ceiling, the IQ score (ratio of developmental age and chronological age) declines while the patient remains unchanged. As the developmental ages did not decrease, we saw in our cohort no indication for regression. An age-related decline in IQ scores is also consistent with the fact that IQ scores described in adult patients with the creatine transporter defect are lower than described in affected children (Hahn et al. 2002). Speech and coordination appear to be specific weaknesses in CRTR-deficient patients and a ceiling appears to be reached earlier than for the other subscales. The age-related decline in IQ scores complicates the evaluation of treatment in children, and further studies of the natural course of the CRTR defect are therefore needed.

No significant increase in brain creatine content upon treatment was seen in $^1$H-MRS. It should be noted that creatine measurements varied inter- and intraindividually, which can be temporarily (mis)taken for improvements. Creatine measurements also differed over the various brain regions, being significantly higher in the basal ganglia and cerebellum than in cortex and white matter. These differences must be taken into account when comparing $^1$H-MRS creatine levels in a single individual or in small numbers of observations. The regional differences are comparable to those in healthy subjects (Pouwels et al. 1999).

There are several possible explanations why treatment failed to increase cerebral creatine content. It is possible that the uptake of arginine and glycine through the blood-brain barrier was insufficient. In future trials, this could be monitored by measurements of cerebrospinal fluid concentrations of amino acids. Other explanations are related to the central question why the CRTR defect leads to cerebral creatine deficiency to begin with if the brain is capable of endogenous creatine synthesis. It is possible that the cerebral creatine synthesis is limited and that the expected upregulation of the AGAT reaction, the rate-limiting step in creatine synthesis, by decreasing creatine (Wyss and Kaddurah-Daouk 2000) or by supplementation of precursors L-arginine and glycine, does not occur in the brain. This is, however, in contrast with the hypothesis that the CNS mainly derives its creatine from endogenous synthesis (Braissant et al. 2001) because the permeability of the blood-brain barrier for creatine appears limited (Wyss and Schulze 2002), and astrocytes, contacting the capillary endothelial cells forming the blood-brain barrier, do not express CRTR (Braissant et al. 2001). In addition, CRTR might also be important in the cerebral creatine synthesis. Braissant et al. found that AGAT and GAMT, although expressed in all CNS cell types, are rarely co-expressed within the same cell and hypothesized that GAA must be transported by CRTR between brain cells for creatine synthesis to occur (Braissant and Henry 2008; Braissant et al. 2007, 2010). In this model GAA accumulation would be
expected in cases of CRTR deficiency (Braissant and Henry 2008), which was indeed suggested in one patient (Sijens et al. 2005). Arginine and glycine supplementation would then not lead to the aimed for creatine increase but to further GAA accumulation, an adverse effect because GAA is considered to be epileptogenic (Tachikawa et al. 2008). However, we saw no GAA accumulation in our cohort of CRTR-deficient patients nor an increase during treatment.

It is possible that our treatment has been effective outside the brain, for instance on muscle function. The temporary improvements in motor skills may have been caused by improved muscle function. Unfortunately, formal muscle function tests were not performed. An increase in body weight has been noted upon creatine monohydrate treatment in patients with the CRTR defect (Anselm et al. 2005; Poo-Arguelles et al. 2006). Five patients in our study showed an increase of more than one to two SD scores in height and weight, although not statistically significant in the whole group.

Our follow-up has been too short to decide whether the treatment might prevent complications later in life, such as myopathy and intestinal dysfuntion, which have been described in adult patients (Kleefstra et al. 2005; Hahn et al. 2002). Personal observations of creatine monohydrate plus L-arginine and glycine treatment in four male adult patients aged between 17 and 54 years registered positive effects with improved behavior in all, amelioration of severe constipation in one, and achievement of urinary continence in another (Mancini, unpublished).

Though this study represents the largest and longest treated cohort so far and includes repeated neuropsychological assessments and repeated brain 1H-MRS, there are still several limitations that should be addressed in future studies. The cohort was heterogeneous in age at the start of treatment. This complicates the evaluation of treatment because neuropsychological assessments may be less reliable in the first years and IQ scores may decline with age as we noticed for certain subscales. Furthermore it is possible that treatment starting at a younger age is more successful. Due to the sample size, this could not be evaluated in this study. The treatment conditions in the cohort differed in the addition of glycine, and neuropsychological assessments and brain 1H-MRS were performed at different treatment durations. This limited the power of the statistical analyses. The analyses were performed irrespective of compliance because the compliance could not be optimally monitored.

In future therapeutic trials, additional or other treatment options need to be considered. S-adenosylmethionine (SAMe) supplementation might be another way to strengthen the cerebral creatine synthesis. SAMe acts as methyl donor in the GAMT reaction, which in fact accounts for the main percentage of total utilization of methyl groups in the body (Wyss and Kaddurah-Daouk 2000). SAMe crosses the blood-brain barrier and increases cerebral phosphocreatine (Moxon-Lester et al. 2009). Folic acid and vitamins B6 and B12 could be added to increase methionine synthesis and maintain low concentrations of S-adenosylhomocysteine, which inhibits GAMT (Moxon-Lester et al. 2009). Other alternative treatment could be with lipophilic creatine analogs, which cross the blood-brain barrier independent of the CRTR. Uptake of lipophilic creatine analogs was found in CRTR-blocked mouse hippocampal slices (Lunardi et al. 2006) and in human CRTR-deficient and control fibroblasts, however no effect of treatment with creatine ethyl ester (CEE) was found in CRTR patients (Fons et al. 2010).

It is possible that creatine is released from central neurons and acts as a neuromodulator (Almeida et al. 2006). Therefore CRTR might also be essential for creatine reuptake and termination of synapsis (Peral et al. 2010) and/or for release of creatine from neurons (Mak et al. 2009). Treatment directed at increasing the levels of creatine might not solve disturbed neuromodulation in CRTR deficiency.

Acknowledgements We thank Ofir T. Betsalel for his help with the figures.

Funding The work of Gajja S. Salomons is supported by the Dutch Society for Scientific Research (ZonMW/NWO), VIDI grant number 917.56.349.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

Almeida LS, Verhoeven NM, Roos B et al (2004) Creatine and guanidinoacetate: diagnostic markers for inborn errors in creatine biosynthesis and transport. Mol Genet Metab 82(3):214–219

Almeida LS, Salomons GS, Hogenboom F, Jakobs C, Schoffelmeer ANM (2006) Exocytotic release of creatine in rat brain. Synapse 60(2):118–123

Anselm IA, Alkuraya FS, Salomons GS et al (2006) X-linked creatine transporter defect: a report on two unrelated boys with a severe clinical phenotype. J Inherit Metab Dis 29(1):214–219

Anselm IA, Coulter DL, Darras BT (2008) Cardiac manifestations in a child with a novel mutation in creatine transporter gene SLC6A8. Neurology 70(18):1642–1644

Bizzi A, Bugiani M, Salomons GS et al (2002) X-linked creatine deficiency syndrome: a novel mutation in creatine transporter gene SLC6A8. Ann Neurol 52(2):227–231

Braissant O, Henry H (2008) AGAT, GAMT and SLC6A8 distribution in the central nervous system, in relation to creatine deficiency syndromes: a review. J Inherit Metab Dis 31(2):230–239
