Case Report

Uridine monophosphate (UMP)-responsive developmental and epileptic encephalopathy: A case report of two siblings and a review of literature

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ABSTRACT

Developmental and epileptic encephalopathy type 50 is an autosomal recessive disorder caused by pathogenic variants in *CAD*. This gene encodes a multifunctional enzyme involved in the initial steps of *de novo* pyrimidine synthesis. Uridine treatment has been shown to be effective in this disease. Here, we report two siblings with *CAD* pathogenic variants who presented with developmental regression and intractable epilepsy. Treatment with oral uridine monophosphate (UMP) resulted in remarkable and rapid clinical improvement in terms of developmental progress and seizure control. We also reviewed previous literature and summarized all reported patients to date.

1. Introduction

Developmental and epileptic encephalopathies (DEE) are a group of disorders characterized by devastating developmental, behavioral, and cognitive impairments that could be associated with intractable epilepsy [1]. Recognition of the specific underlying etiology is of utmost importance as some might be amenable to targeted, etiology-specific treatment. In addition, some medications can aggravate certain diseases. Recent advances in molecular testing with increased utilization of next generation sequencing (NGS) have uncovered an expanding list of genes associated with several neurodevelopmental disorders.

Amongst the various treatable DEEs is the recently described CAD deficiency [2]. CAD is a multifunctional enzyme complex that catalyzes the first three steps in the *de novo* pyrimidine biosynthesis pathway. The end-products of this pathway are the pyrimidine nucleotides: uridine triphosphate (UTP) and cytosine triphosphate (CTP). These nucleotides are essential for DNA and RNA synthesis and are also important in protein glycosylation, polysaccharide synthesis, and lipid metabolism [3]. Alternatively, UTP and CTP can be obtained directly from uridine through the pyrimidine recycling pathway [4]. Following the enzyme's discovery in 1977, considerable advancements have been made in uncovering the mechanisms by which cellular pyrimidines are regulated

to meet the needs of the cell [5,6].

In 2015, Ng et al. reported a patient with biallelic pathogenic variants in *CAD* who presented at 17 months of age with refractory epilepsy [2]. Uridine was suggested as a potential therapy for this new glycosylation disorder. Subsequent studies supported the positive response to uridine in this condition [7–12]. Tri-acetyl uridine, uridine and UMP have all been used. In this report, we present two siblings with a pathogenic homozygous variant in *CAD,* who presented with developmental regression after seizure onset. Treatment with oral uridine monophosphate (UMP) showed prompt cessation of seizure activity and substantial developmental progress.

2. Case report

Patient one (proband) is a 14-year-old male who was born at term after uncomplicated pregnancy and delivery to healthy parents who are first cousins. Mild fine motor and language delay were noted early. At the age of three years, he started to have generalized tonic-clonic (GTC) seizures. He later developed left-sided focal seizures with post-ictal Todd's paralysis. At four years of age, he was admitted to the pediatric intensive care unit (PICU) with status epilepticus. Over time, he eventually developed intractable seizures of several types (GTCs, focal,

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myoclonic, and atonic) and progressive unsteadiness and gait difficulties over the following years. He also developed speech difficulties, inattention, and arrested development. Several anti-seizure drugs (ASDs) were used, namely valproate, carbamazepine, clobazam, and levetiracetam, with no success. His blood smear demonstrated mild anemia (hemoglobin 10.8 g/dl; reference value 11-15 g/dl), poikilocytosis, and anisocytosis.

Upon exam, he was noted to have esotropia in right eye, intention tremor and dysarthria as well as wide-based gait. Electroencephalogram (EEG) suggested frequent multifocal spikes and diffuse slowing of the background (Fig. 1a). Brain magnetic resonance imaging (MRI) demonstrated cerebellar atrophy (Fig. 2).

Patient two, the younger sibling of patient one, is currently a six-year-old boy. He was born at term after an uneventful pregnancy and delivery. He had a mild delay in cognition, language, and motor

function. At three years of age, he developed his first seizure. It was focal, right hemiclonic, and soon after became recurrent and frequent. When first evaluated at three years of age, he was able to walk up and down stairs, ride his tricycle, kick, and catch a ball. He could say his name and was able to speak two-word sentences. He could not use a spoon nor was he able to dress or undress himself. On physical examination, he had mild hypotonia, dysmetria, and hyperactivity. The first EEG performed revealed background slow activity, abundant generalized 3-Hz spike-and-wave discharges with left frontal predominance, as well as multifocal sharp wave discharges, predominantly originating from the left hemisphere. Brain MRI showed cerebellar atrophy. Blood smear indicated poikilocytosis and anisocytosis without anemia (hemoglobin 13.9 g/dl; reference value 11-15 g/dl).

Over the subsequent year, he developed intractable daily seizures with several other semiologies (staring spells, atonic, and myoclonic
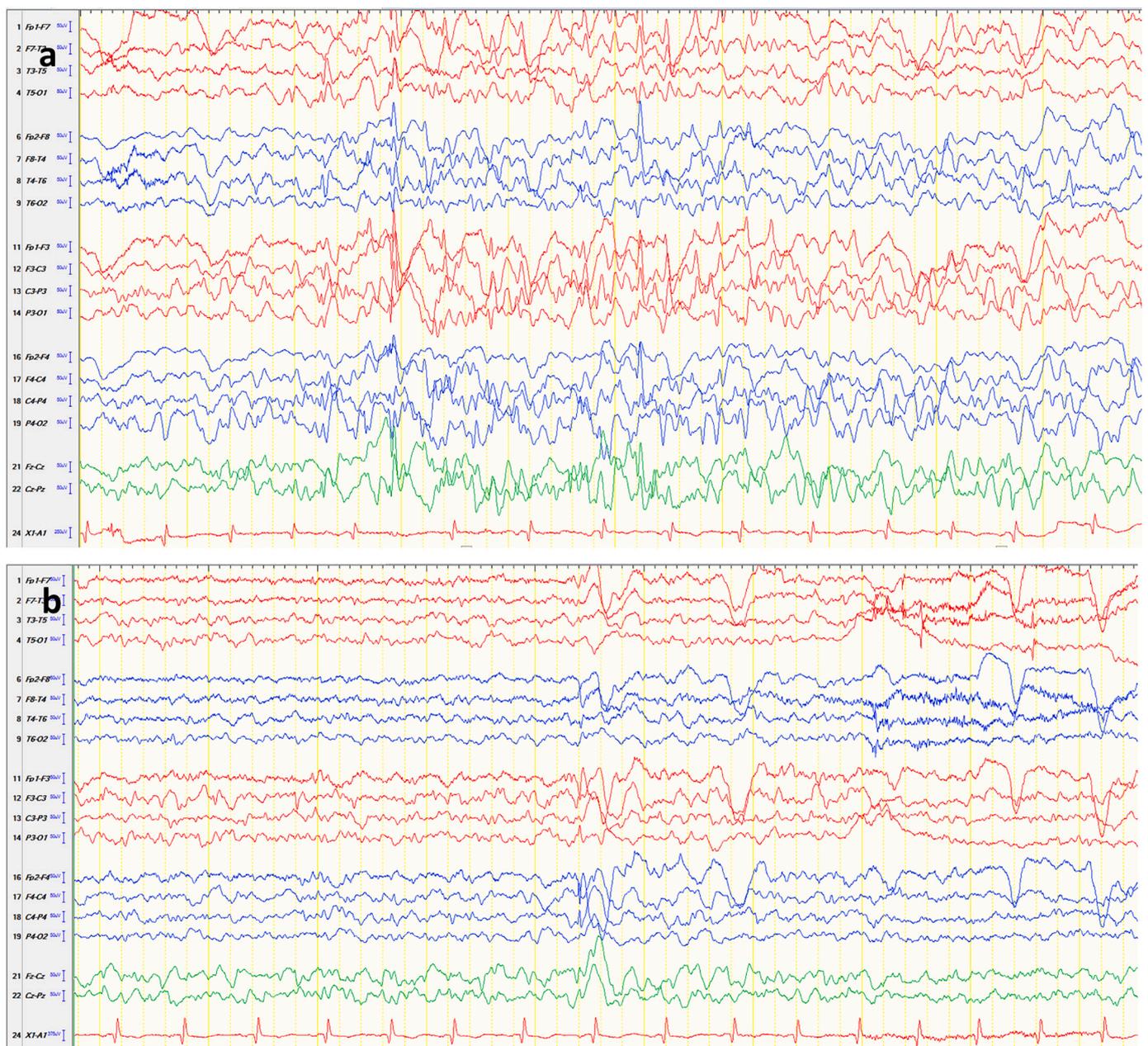
Fig. 1. a. EEG of patient one at the age of 10 prior to uridine treatment. Background slowing is evident with multifocal spikes and sharp waves. Settings: Sensitivity = 10, HFF = 70, LFF = 0.5.
b. Follow-up EEG for patient one following uridine treatment. Improved background activity can be appreciated, as well as a marked reduction in the multifocal epileptiform discharges previously seen. Settings: Sensitivity = 10, HFF = 70, LFF = 0.5.

Fig. 2. Brain MRI of patient one. Mild to moderate cerebellar atrophy and diffuse mild supratentorial brain tissue volume loss.

seizures, in addition to his focal seizures) despite trials of several anti-seizure medications (valproate, carbamazepine, phenobarbital, and levetiracetam). He also developed progressive deterioration in balance and independent ambulation. An episode of status epilepticus at the age of 3.5 years led to a prolonged hospitalization in the PICU at an outside facility where he sustained cardiac arrest requiring prolonged cardio-pulmonary resuscitation (CPR). Subsequently, he suffered hypoxic-ischemic brain insult, spastic quadriplegia, and worsening seizures. Two-stage functional hemispherectomy was then performed to control his debilitating seizures, which improved then (from up to 50 seizures daily to less than two seizures a month) and his anti-seizure medications were reduced to carbamazepine and valproate. Despite this improvement, and due to his complicated clinical course, he eventually had a profound deterioration in his developmental skills; he became bed-bound, non-verbal, spastic quadriplegic, and encephalopathic.

Whole exome sequencing (WES) identified a homozygous, potentially pathogenic variant in *CAD* (c.5959C>G; p.(Leu1987Val)) in both siblings. Segregation analysis demonstrated that the parents were carriers. A complementation study performed by del Caño-Ochoa et al. confirmed this variant as deleterious for CAD activity and suggested uridine as a potential therapy [13].

3. Treatment with UMP

Oral UMP (130 mg/kg/day in three daily doses) was commenced based on previous recommendations [14].

The older sibling displayed a more pronounced response to UMP with complete cessation of seizures two days after initiating the treatment. He remained seizure-free over a follow-up period of five months. Considerable progress in his functional skills was observed. Currently, he can ambulate independently, run, ride a bicycle, and communicate with clear sentences. His follow-up EEG showed marked reduction in epileptiform discharges (Fig. 1b). His anti-seizure medications are reduced to levetiracetam monotherapy.

As for the younger child, after one month of treatment with UMP he

was able to move his limbs spontaneously against gravity and had become less spastic. He was noted to be more alert and conscious and started to cry and withdraw to painful stimulus. Seizure frequency and intensity have reduced dramatically, and his ASDs were gradually withdrawn. Currently, he is on valproic acid and lacosamide. A follow up EEG five months after treatment with UMP showed marked reduction in the formerly seen epileptiform discharges. Peripheral blood smear revealed normalization of the anisocytosis and poikilocytosis. On the last clinic evaluation at six years of age and after five months of treatment with UMP, he continued to have better control in his epilepsy and advances in his functional skills albeit he remained encephalopathic. This is chiefly attributed to the secondary hypoxic-ischemic injury he sustained.

4. Discussion

CAD developmental and epileptic encephalopathy 50 is an autosomal recessive neurodegenerative disease that presents with early-onset developmental delay, refractory epilepsy, and dyserythropoietic bone marrow with or without anemia. Following the initial description of the disease in 2015, several cases were described. A summary of these cases is provided in Table 1. Patients with CAD deficiency manifested primarily with neurologic and hematologic abnormalities. All reported cases had infantile-onset seizures (one study reported neonatal onset [11]), often of multiple types; focal, generalized tonic-clonic, myoclonic, absences, tonic and atonic. Seizures are intractable to conventional drug therapy, as well as other modalities of treatment; including use of cannabidiol [10], ketogenic diet [8] and surgery [12]. Patients had marked hematological involvement with peripheral blood smears demonstrating anisopoikilocytosis. Some patients developed severe anemia requiring blood transfusion [8].

The developmental delay was a consistent feature in all patients. Most patients had initial normal development prior to the seizure onset with subsequent regression, predominantly observed in language and cognitive domains. Progressive ataxia leading to eventual loss of

Table 1

Summary of the clinical features, laboratory, EEG, and MRI findings of all reported cases of CAD deficiency. BG: background; DD: developmental delay, GI: gastrointestinal; GTC: generalized tonic clonic,. NA: not available, *: The clinical features are for 10 individuals only; two of them are described in details in this report (case 1 and 2 in the table).

Reference	No.	Gender	Age at seizure onset	CAD variant	Clinical features	Types of seizure	Blood smear	EEG findings	Brain MRI findings	Uridine therapy	Clinical outcome
This report	1–2		3 years	(c.5959C>G; p. (Leu1987Val)	DD, seizures, ataxia, hypotonia	Myoclonic-atonic, absence, GTC	Anemia, anisopoikilocytosis		Cerebellar atrophy	+	Improvement of ambulation, cognition, and resolution of seizures. Second patient improved encephalopathy and seizure control
Ng et al. [2]	3	Male	17 months	c.1843-1G>A; c.6071G>A	DD, seizures, hypotonia, ataxia	NA	anisopoikilocytosis	NA	Normal	−	NA
Koch et al. [7]	4	Male	20 months	c.98 T>G Hom	DD, encephalopathy, seizures, ataxia, tremor	GTC	Anemia, anisopoikilocytosis.	NA	Cerebral atrophy	−	Deceased at 4 years.
	5	Female	2 years	c.98 T>G Hom	DD, seizures	GTC	Anemia, anisopoikilocytosis	Multifocal sharp waves.	NA	+	Cessation of seizures, resolution of the
	6	Female	6 months.	c.1843-3C>T; c.5365C>T	DD, encephalopathy, seizures, hypotonia, nystagmus	GTC	Anemia, Anisopoikilocytosis.	Slow BG, multifocal discharges, periodic patterns.	Cerebral atrophy	+	encephalopathy, regain of ambulation, and normalization of anemia.
	7	Male	2 years	c.1843-1G>A; c.6071G>A	DD, encephalopathy, seizures, ataxia	GTC, focal, febrile	Anemia, anisopoikilocytosis.	NA	Cerebral atrophy	−	Deceased at 5 years.
Zhou et al. [8,9]	8	Male	18 months	c.108delC;c.3775G>A	DD, seizures, visual impairment	Focal, myoclonic	Anemia, anisopoikilocytosis	Generalized 3-Hz Spike-and -wave	Cerebral and cerebellar atrophy	+	Cessation of seizures, regain of ambulation and development, and normalization of anemia.
	9	Female	7.5 months	c.3676G>T; c.2944G>A	DD, seizures, hypotonia, abnormal VEP.	Focal	Anemia, anisopoikilocytosis	Focal discharges.	Cerebral atrophy	+	Cessation of seizures, regain of developmental
	10	Female	8 months	c.4549G>C; c.64216422insTGCT	DD, seizures, abnormal VEP.	Focal to secondary generalized	Mild anemia	Focal discharges	Normal	+	progress, resolution of IIED on EEG, and normalization of anemia.
Kamate et al. [11]	11	Male	4 days	c.239G>T Hom	DD, seizures	Focal, GTC, myoclonic	Anemia	Slow BG, multifocal discharges	Normal	+	Improvement of seizures, developmental progress, and resolution of IIED on EEG.
Russo et al. [15]	12	Male	NA	c.5366G > A Hom	DD, autistic behavior, seizures	Drop attacks, focal, GTC	Anemia, anisopoikilocytosis	Multifocal discharges	Normal	+	Cessation of seizures, regain of developmental progress, resolution of IIED on EEG, and normalization of anemia.
Rymen et al. [14]	13	Female	NA	c.2900A>G Hom	DD	No seizures	Anemia	NA	NA	NA	NA
	14	Male	NA		DD	No seizures	Anemia	NA	NA	NA	NA
	15	Female	6 years	c.2617_2620delGACA Hom	DD, autistic behavior, seizures, ataxia	NA	Anemia	NA	NA	NA	NA
	16	Female	23 months	c.98 T>G Hom	DD, seizures, ataxia	NA	Anemia	NA	Cerebellar atrophy	+	Cessation of seizures, regain of ambulation, and normalization of anemia.
	17	Male	7 years		DD, seizures	NA	Anemia	NA	Normal	+	Slight improvement in alertness, and normalization of anemia.
	18	Male	3 years		DD, seizures, ataxia	NA	Anemia	NA	Cerebral and cerebellar atrophy	+	Transient improvement in seizure control, normalization of anemia, and virtually no effect on development.

Table 1 (*continued*)

Reference	No.	Gender	Age at seizure onset	CAD variant	Clinical features	Types of seizure	Blood smear	EEG findings	Brain MRI findings	Uridine therapy	Clinical outcome
	19	Male	2 years	c.4397-209 T>G; c.6071G>A	DD, encephalopathy, seizures, ataxia, hyperkinesia, dystonia, tremor	NA	Anemia	NA	NA	+	Improvement of seizures, developmental progress, regain of ambulation, and normalization of anemia.
	20	Female	3 months	c.3194G>A; c.5860G>A	DD, seizures, ataxia	NA	Anemia	NA	NA	NA	NA
	21	Female	4 years		DD, ataxia, tremor	NA	Anemia	NA	NA	NA	NA
	22	Female	3 years	c.2843G>A; c.2284G>A	DD, seizures, ataxia, tremor	NA	Anemia	NA	Normal	+	Tremor and ataxia nearly resolved, developmental progress, near normalization of anemia.
	23	Male	3 days	c.2995G>A Hom	DD, seizures, hypotonia	NA	NA	NA	Normal	NA	NA
	24	Male	8 months	c.223-2A>G; c.5429G>A	DD, encephalopathy, seizures	NA	Anemia	NA	Cerebral and cerebellar atrophy	+	Cessation of seizures, but no effect on EEG, slight improvement in development, and normalization of anemia.
	25	Female	2 months	c.178 T>C Hom	DD, seizures	NA	Anemia	NA	NA	+	Improvement of seizures, developmental progress, and normalization of anemia.
Frederick et al. [10]	26	Female	8 years	c.98 T > G Hom	DD, autism, encephalopathy, seizures, nystagmus, ataxia, tremor	Focal, tonic, GTC, absence	Anemia, thrombocytopenia,	Diffuse slowing, multifocal discharges	Normal.	+	Cessation of seizures, resolution of encephalopathy, and regain of developmental progress.
McGraw et al. [12]	27	Female	3.5 years	c.5296_5308del13; c.5429G > A	DD, autism, seizures, hypotonia	GTC, myoclonic, focal motor with postictal paresis, atonic, absence	Anisopoikilocytosis	BG slowing, generalized spike-and-slow wave	Mild cerebellar atrophy	+	Improvement of seizures, developmental progress, improvement of IIED on EEG, and normalization of anemia.
	28	Male	2 years	c.5296_5308del13; c.5429G > A	DD, seizures	Atonic, GTC	NA	Disorganized BG, tonic seizures correlating with paroxysmal fast activity	Cerebellar atrophy	+	Improvement of seizures, developmental progress.
Del Caño-Ochoaet al [13].	29–51	NA	NA	c.2156 + 5G>A; c.4667A>C c.5147C>T; c.5561G>A c.2372A>C; c.4487G>C c.713G>A; c.1159G>A c.4501 T>A; c.6556C>T c.419A>G; c.5570G>A c.943G>A; c.5353C>T c.785 T>C; c.3868G>A c.5147C>T; c.5561G>A c.3649G>A; c.4568C>T	Intellectual disability/ developmental delay (100%); seizures (90%); feeding problems (50%); hypotonia (50%); ataxia or gait problems (50%); facial dysmorphism (50%);GI abnormalities (50%); anemia (40%); skeletal abnormalities (30%); cardiac abnormalities (20%) *	NA	NA	NA	NA	NA	NA

Table 1 (*continued*)

Reference	No.	Gender	Age at seizure onset	CAD variant	Clinical features	Types of seizure	Blood smear	EEG findings	Brain MRI findings	Uridine therapy	Clinical outcome
				c.959A>G; c.2984C>G							
				c.1576G>A Hom							
				c.5959C>G Hom							
				c.5959C>G Hom							
				c.6329G>T Hom							
				c.3098G>A Hom							
				c.5957G>A Hom							
				c.6382G>A Hom							
				c.3512C>A; c.4315-1G>A							
				c.2995G>A Hom							
				c.98 T>G Hom							
				c.713G>A Uniparental disomy Chr. 2							
				c.4669C>G; c.6320C>G							
				c.2386C>A; c.4735G>A							
				c.887G>A; c.2225G>A							

ambulation was observed in most patients including our patients. This observation combined with the cerebellar atrophy seen on brain MRI suggests a predilection of the disease to affect the cerebellum. Uridine therapy resulted in significant clinical improvement in all patients in terms of progression of development, seizure control, normalization of the anemia and hematological abnormalities, and prevention of cerebellar atrophy.

The variant c.5959C>G p.(Leu1987Val) identified in our patients is located in the active site of aspartate transcarbamylase (ATCase) domain of CAD that has a low rate of benign missense variants. Using complementation assay, this variant failed to rescue or partially rescued the growth of these cells in a culture media deprived of uridine [13].

Treatment with UMP in our subjects resulted in immediate clinical improvement and amelioration of symptoms. It was a well-tolerated in our patients and no adverse effects have been noted over a follow-up period of five months.

5. Conclusion

CAD deficiency is a treatable developmental and epileptic encephalopathy that presents in infancy with developmental regression, epilepsy with multiple seizure types, ataxia, and anisopoikilocytosis. There are no reliable metabolic biomarkers for this disease; although the majority of patients display dyserythropoiesis, this is not specific. Currently, the only means for diagnostic confirmation is through NGS techniques combined with a functional assay[22]. Given that it is recently recognized, *CAD* may not be included in all epilepsy panels. Without treatment, the disease can lead to catastrophic developmental and functional impairments and potentially death. Supplementation with uridine is vital to prevent disease progression. Therefore, a high index of suspicion is needed in patients presenting with intractable epilepsy and developmental delay of unclear cause. A trial of uridine supplementation is worth attempting in such cases, since no deleterious effects are known. However, without functional confirmation, families should be made aware of the uncertainty.

Declaration of Competing Interest

We have no relationships with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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