A successful treatment with uridine in CAD related disorders

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BACKGROUND

CAD related developmental and epileptic encephalopathy is an autosomal recessive neurodegenerative disorder caused by pathogenic variants in CAD gene that encode a multifunctional enzyme complex catalyzes the first three steps in the de novo pyrimidine synthesis.
This disorder was recently reported, and several studies have demonstrated that treatment with uridine is beneficial.
Exome sequencing in one family identified a biallelic, novel and pathogenic variants c.5959C>G p.(Leu1987Val) in CAD gene in two siblings who presented with developmental regression after seizure onset. Segregation analysis demonstrated that the parents were carriers. Complementation study performed by del Caño-Ochoa et al. identified this variant as deleterious for CAD activity and suggested uridine as a potential therapy in this disorder.
In this article we demonstrated that treatment with oral uridine resulted in remarkable improvement rendering this disorder as one of the few treatable neurometabolic diseases.

CASE REPORT

Patient 1(proband), a 6-years old boy, is the fourth child born to healthy consanguineous parents. He had a mild delay in cognition, language, and motor function. At 3 years of age, he developed his first focal seizure and soon after became recurrent and frequent. When first evaluated at three years of age, delays in language and fine motor development were recognized. On exam he had normal growth parameters, 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. Brain MRI showed cerebellar atrophy. Blood smear indicated poikilocytosis and anisocytosis without anemia (hemoglobin 13.9g/dl; reference value 11-15g/dl). Over the subsequent year, he developed intractable daily seizures, profound deterioration in his developmental skills; he became bed-bound, non-verbal, spastic quadriplegic, and encephalopathic.

Patient 2: a 14-year-old male, born at term after uncomplicated pregnancy and delivery to a healthy consanguineous parents. He had a relatively normal development, with mild fine motor and language delay, until the age of 3 years when he started to have generalized tonic clonic (GTC) seizures. He later developed left-sided focal seizures with post-ictal Todd's paralysis. At 4 years of age, he was admitted to the PICU for seizure control. His clinical course was slow, but he eventually developed intractable seizures of several types (GTCs, focal, myoclonic, and atonic) and progressive unsteadiness, gait difficulties, speech difficulties, inattention, and arrested development over the following years. Several anti-seizure medications (ASDs) were used with no success. Upon exam, he was noted to have squint, dysmetria and dysarthria as well as intension tremor and wide-based gait. EEG suggested frequent multifocal spikes and background slowing (Figure 1). Brain MRI demonstrated cerebellar atrophy (Figure 2).

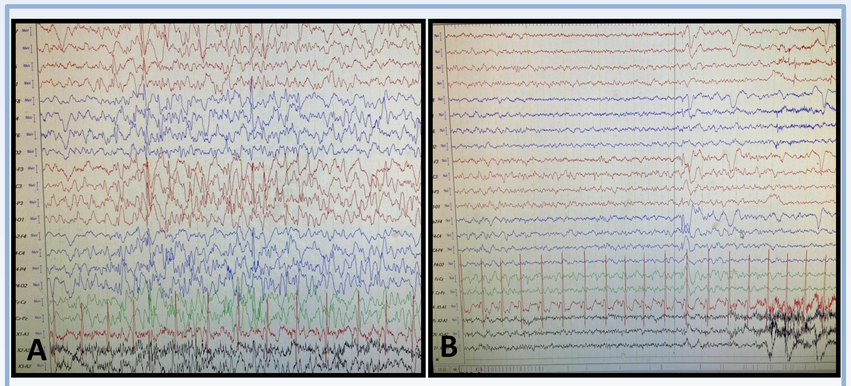

Figure 1. A- EEG of patient 2 at the age of 10 prior to uridine treatment. Background slowing is evident with multifocal spikes and sharp waves. Settings: Sensitivity= 10 µV/mm, HFF=70 Hz, LFF=0.5 Hz. B- follow-up EEG following uridine treatment showed marked reduction in the epileptic discharges

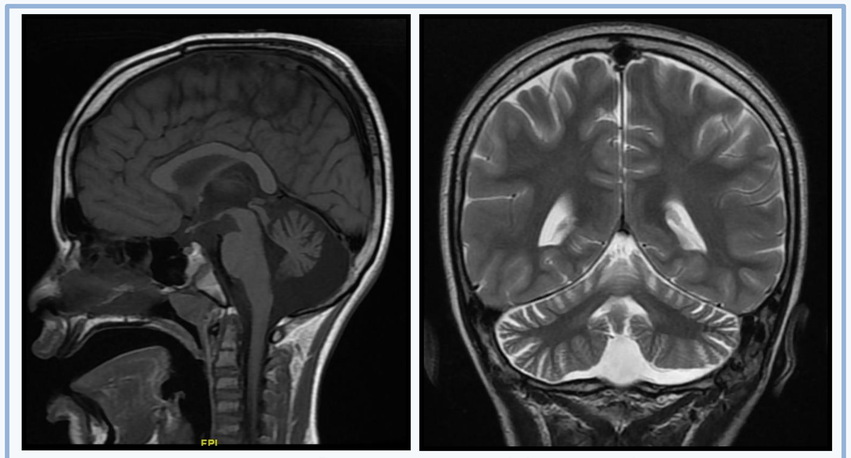

Figure 2. Brain MRI of patient 2. Mild to moderate cerebellar atrophy and diffuse mild supratentorial brain tissue volume loss.

RESULT

Studies have shown that early treatment of this condition with uridine led to immediate cessation of seizure, improve outcome, and prevent fatal and irreversible complications. Based on this finding we started uridine monophosphate (130 mg/kg/day in three daily doses)
Patient 1: After one month treatment with uridine, the child started to move his limbs spontaneously against gravity and had become less spastic. He was noted to be more alert and conscious and start to cry and withdraw to painful stimulus. Seizure frequency and intensity have reduced markedly, and his ASDs were gradually withdrawn. Currently, he is on valproic acid and lacosamide. A follow up EEG at five months after the treatment showed marked reduction in the epileptic discharges . Peripheral 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 uridine, 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.
Patient 2 displayed a more pronounced response to uridine with complete cessation of seizures two days after initiating the treatment. He remained seizure free over a follow up period of five months. A 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 the epileptiform discharges (Figure 2: B). His ASDs are reduced to levetiracetam monotherapy

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, however, peripheral blood smear could serve as a useful screening tool since most of the patient display dyserythropoiesis. Currently, the only mean for diagnostic confirmation is through whole exome sequencing (WES). Inclusion of CAD gene in epilepsy panels would be efficient and cost-effective since numerous centers do not have access to WES. 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.

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