Metabolic Or Ischemic Stroke in Succinic Semi-Aldehyde Dehydrogenase Deficiency Due to the Homozygous Variant c. 1343 + 1_1343 + 3delGTAinsTT in ALDH5A1

Sir,

With interest we read the article by Yoganathan *et al*. about a 15-month-old female with succinic semi-aldehyde dehydrogenase deficiency (SSADH), manifesting with developmental delay and language deficits, who experienced an acute-onset right hemiparesis due to a "metabolic stroke" with MRI hyperintensity on diffusion-weighted imaging (DWI) and hypointensity on corresponding apparent diffusion coefficient (ADC) maps. The lesion was interpreted as "stroke-mimic" as it had disappeared on follow-up MRI. We have the following comments and concerns.

Comment I: It remains unclear what the authors mean with "metabolic stroke". Do they mean an ischemic stroke in a patient with a metabolic disorder or do they mean a stroke-like episode (SLE), as frequently seen in various mitochondrial disorders (MIDs). Differentiation between these entities is crucial as treatment and outcome vary considerably between the two.

Response: We have reported a 15-month-old child with succinic SSADH, presenting with a predominant delay in socio-personal and language milestones and acute onset right hemiparesis following an intercurrent infection.[1] Stroke is defined as "rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent nonvascular cause".[2] Zinnanti *et al*. have described metabolic stroke as "rapid onset of lasting central neurological deficit associated with decompensation of an underlying metabolic disorder" and it occurs in the absence of blood vessel occlusion or rupture.[3] Though metabolic disturbances in systemic illnesses such as diabetes, renal or hepatic failure may result in stroke, the terminology of "metabolic stroke" has been often used in patients with inherited disorders.[4] The pathophysiology mechanisms in metabolic stroke are variable and there may be overlapping mechanisms that remains poorly understood. Thromboembolism, hemorrhage, angiopathy with poor vasodilatation, hyperexcitability of neurons, and energy failure are few mechanisms that predispose to focal neurological deficits in children with underlying metabolic disorders.[4,5] Organic aciduria and aminoacidopathies are known to cause to focal neurological deficits during metabolic decompensation.[4] Signal changes on neuroimaging of these patients have predilection for basal ganglia and are not confined to a particular vascular territory. Our patient with SSADH deficiency presented with focal neurological deficit following a diarrhoeal illness and also had a premorbid developmental delay.[1] Hyperintensity with diffusion restriction was observed in the left globus pallidus in our case, thus not confining to a defined arterial territory. Studies on murine models found that an elevated gamma-hydroxybutyrate in SSADH deficiency may lead to oxidative stress.[6] The other mechanisms that have been described in SSADH deficiency are myelin abnormalities, mitochondrial dysfunction, alteration in intermediary metabolism, bioenergetics alteration, and depletion of neurosteroid.[7] The neurological and imaging findings in our case may be speculated to result from oxidative stress, alteration in intermediary metabolism, and altered bioenergetics, as the exact mechanisms are unclear. We have also explained in our case report that the underlying oxidative stress might have been worsened by an intercurrent infection leading on to focal neurological deficit and the recovery from hemiparesis could probably be explained by an improvement from catabolic state.[1]

Comment II: According to the MRI images provided in Figure 1 the lesion looks as ischemic why it is curious that the authors classify the event as "stroke-mimic". Hyperintensity on DWI and corresponding hypointensity on ADC suggest cytotoxic edema and thus ischemic stroke. We should know after which interval the lesion completely disappeared and if any dynamic changes were observed until disappearance.

Response: We have mentioned that MRI brain done at presentation showed hyperintensity of left globus pallidus with cytotoxic edema. Though cytotoxic edema is commonly seen associated with ischemic stroke, many other nonischaemic conditions also cause cytotoxic edema primarily due to energy failure or depletion.[8] It has been well described in

organic acidemia and other metabolic disorders.[8] Hence, the cytotoxic edema seen in our patient with underlying SSADH deficiency could possibly be related to neurotoxicity resulting from elevated gamma-hydroxybutyrate. Ischaemic stroke due to vascular occlusion is less likely, as it is not confined to a defined arterial territory. Though bilateral and symmetrical lesions of globus pallidi are reported in children with SSADH deficiency, asymmetrical involvement have also been described in literature.[9] The imaging findings in SSADH deficiency have been clearly discussed in our case report.[1] Multiple serial MRI scans to look for dynamic changes were not attempted in our patient because there was no progression or recruitment of neurological symptoms and also considering the risk related to use of anesthetic agents for sedation. Our patient was under regular follow-up and a repeat brain MRI was done at 2 years of age.

Comment III: Treatment of ischemic stroke is well established, whereas the treatment of a SLE is under debate. Depending on the pathophysiological hypothesis some experts recommend application of antiepileptic drugs (AEDs) irrespective if patients present with clinical seizures or epileptiform discharges on electroencephalography (EEG), whereas other propose the application of L-arginine, antioxidants, or steroids. We should know which treatment the index patient received and if the treatment was effective or not.

Response: As the diagnosis of SSADH deficiency was clearly established in our patient, she was managed with vigabatrin. In addition, our patient also received physiotherapy, occupational therapy and speech therapy. Our patient had shown significant developmental gains on a regular follow-up assessment but hypotonia persisted. These clinical data have been clearly mentioned in our case report.[1] Vigabatrin is a GABA transaminase inhibitor and has been tried in children with SSADH deficiency.[10] The role of L-arginine, or steroids has not been established in the management of children with SSADH deficiency. Antioxidant therapy appears to have a potential role based on studies in the murine models.[6]

Comment IV: Though the patient did not present with clinical seizures and though the EEG was normal, vigabatrin was given. Since effectivity of vigabatrin for seizures in SSADH is questionable and since the patient never exhibited seizures, the authors should explain upon which rationale vigabatrin was applied. If the rationale was blocking of the GABA breakdown, as has been previously proposed, this should explicitly mentioned in the discussion. Missing in the report is a discussion whether the mild clinical improvement was attributed to vigabatrin or was interpreted as spontaneous recovery from the metabolic defect.

Response: Understanding the biochemical pathways in metabolic disorders is crucial for appropriate management. We have discussed about the metabolic pathway in children with SSADH deficiency in our case report.[1] In patients with SSADH deficiency, succinic semialdehye formed from GABA is not metabolized to succinic acid.[6,10] Succinic semialdehyde is therefore reduced to 4-hydroxybutyric acid resulting in neurotoxicity.[10] Vigabatrin is an irreversible inhibitor of GABA transaminase and thereby decreases the level of 4-hydroxybutyric acid.[10] Hence, our patient was treated with vigabatrin despite no clinical seizures and normal EEG. Vigabatrin has been not only been used to control seizures but also to improve the ataxia, communicative skills, alertness, and behavioural symptoms in patients with SSADH deficiency.[11,12] It has been mentioned briefly in the discussion part of our case report.[1] Variable response to vigabatrin treatment has been reported in the literature.[12] Our patient had shown mild and significant developmental gains on a follow-up assessment after 6 months and 2 years respectively, as mentioned in our report. The steady clinical improvement could possibly attributed to treatment with vigabatrin in addition to the occupational therapy, physiotherapy, and speech therapy.

Comment V: It is reported that the patient had hyporeflexia but that nerve conduction studies were normal. We should know if the patient also presented with muscle weakness, muscle wasting, elevated creatine-kinase (CK), and a myogenic electromyography (EMG), and if the authors considered myopathy as the cause of hyporeflexia.

Response: Best observed power in our patient on presentation was 3/5 on the left and 2/5 on the right upper and lower limbs. Hypotonia, hyporeflexia, and bilateral extensor plantar responses were observed. These clinical findings were mentioned in our case report.[1] Bulk of muscles was normal and serum creatine kinase was 80 U/L (normal range: 45-195 U/L). Demyelinating neuropathy has been described in a patient with SSADH deficiency.[13] The nerve conduction parameters were normal for age in our case but needle EMG was not done due to poor patient cooperation. Hypotonia with areflexia has been reported previously in patients with SSADH deficiency despite normal nerve conduction and EMG studies.[14] To the best of our knowledge, myopathy has not been reported in genetically confirmed SSADH deficiency cases.

Comment VI: Missing in the report is a presentation of the vascular risk factors. We should know if the individual or family history was positive for arterial hypertension, hyperlipidemia, diabetes, or atrial fibrillation. It should be reported if long-term ECG recording was carried out to exclude paroxysmal atrial fibrillation. We should know the results of the echocardiographic examination.

Response: Family history was noncontributory in our case except for paralytic poliomyelitis in mother and this has been mentioned in our case report.[1] Blood homocysteine and lipid profile were normal in our patient. No prothrombotic risk factors were identified in the initial work-up. Vasculitis screening was negative. Screening for human immunodeficiency virus infection was negative. Cerebrospinal fluid (CSF) analysis including cell count, protein, sugar, and lactate were also normal. CT brain did not reveal any calcification or hemorrhage. Considering the word limit for a case report,

the full panel of laboratory investigations reports were not detailed. Blood pressure and clinical examination of the cardiovascular system were also normal. As the diagnosis of SSADH deficiency was established in our patient based on the analysis of urinary organic acid by gas chromatography-mass spectrometry and mutation analysis of aldehyde dehydrogenase 5 family, member A 1 (*ALDH5A1*) gene, a further work-up with long-term ECG and echocardiography were not performed.

Comment VII: Imaging studies should be revised for cerebellar atrophy, since it has been described as a cerebral manifestation of the disease.

Response: The spectrum of imaging findings in children with SSADH deficiency including cerebellar atrophy has been provided in the discussion part of our case report.[1]

Comment VIII: Overall, this interesting case report has a number of limitations and shortcomings which need to be solved before final conclusions can be drawn.

Response: To conclude, our patient with SSADH deficiency had well-described clinical findings such as developmental delay, language deficits, and hypotonia. Acute onset focal neurological deficit is a novel manifestation in SSADH deficiency.[1] There were no major limitations or shortcomings in the diagnosis, evaluation, and management of our patient with SSADH deficiency.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 28-Apr-2020 **Revised:** 09-May-2020 **Accepted:** 27-May-2020
Published: 28-Apr-2021

DOI: 10.4103/aian.AIAN_360_20