

# Metabolic Stroke: A Novel Presentation in a Child with Succinic Semialdehyde Dehydrogenase Deficiency

Sangeetha Yoganathan, Gautham Arunachal<sup>1</sup>, Lisa Kratz<sup>2</sup>, Mugil Varman<sup>3</sup>, Maya Thomas, Sniya Valsa Sudhakar<sup>3</sup>, Samuel Philip Oommen<sup>4</sup>, Sumita Danda<sup>1</sup>

Departments of Neurological Sciences, <sup>1</sup>Medical Genetics, <sup>3</sup>Radiodiagnosis and <sup>4</sup>Developmental Paediatrics, Christian Medical College, Vellore, Tamil Nadu, India, <sup>2</sup>Biochemical Genetics Laboratory, Kennedy Krieger Institute, Baltimore, Maryland, United States of America

## Abstract

Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal recessive disorder of gamma-aminobutyric acid metabolism. Children with SSADH deficiency usually manifest with developmental delay, behavioral symptoms, language dysfunction, seizures, hypotonia, extrapyramidal symptoms, and ataxia. Diagnosis of SSADH deficiency is established by an abnormal urine organic acid pattern, including increased excretion of 4-hydroxybutyric acid and the identification of biallelic pathogenic variants in aldehyde dehydrogenase 5 family, member A1 (*ALDH5A1*) gene. Here, we describe a 15-month-old girl with SSADH deficiency presenting with developmental delay, language deficits, and acute-onset right hemiparesis, following recovery from a diarrheal illness. Brain magnetic resonance imaging revealed hyperintense signal changes involving the left globus pallidus in T2-weighted images with restriction of diffusion in the diffusion-weighted images. Increased excretion of 4-hydroxybutyric acid, threo-4,5-dihydroxyhexanoic acid lactone and erythro-4,5-dihydroxyhexanoic acid lactone was detected by urine organic acid analysis and a diagnosis of SSADH deficiency was confirmed by the identification of homozygous pathogenic variant in *ALDH5A1*. Stroke mimic is a novel presentation in our patient with SSADH deficiency. She was initiated on treatment with vigabatrin and has shown developmental gains with the recovery of right hemiparesis. Follow-up neuroimaging shows near complete resolution of signal changes in the left globus pallidus, while there was subtle hyperintensity in the right globus pallidus. The phenotypic spectrum of SSADH deficiency is widely expanding, and this disorder should be considered in the differential diagnosis of children with metabolic stroke.

**Keywords:** 4-hydroxybutyric acid, aldehyde dehydrogenase 5 family, member A1 gene, Succinic semialdehyde dehydrogenase deficiency, stroke mimic, vigabatrin

## INTRODUCTION

Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare autosomal recessive disorder of gamma-aminobutyric acid (GABA) metabolism manifesting with developmental delay, language deficits, behavioral symptoms, hypotonia, extrapyramidal symptoms, ataxia, and epilepsy.<sup>[1]</sup> Diagnosis of SSADH deficiency is established by the identification of biallelic pathogenic variants in *aldehyde dehydrogenase 5 family, member A1 (ALDH5A1)* gene. SSADH deficiency shows both intrafamilial and interfamilial phenotypic heterogeneity with a wide spectrum of clinical manifestations and wide age range of presentations.<sup>[1]</sup> Here, we describe a 15-month-old girl with biochemical and molecular confirmation of SSADH deficiency presenting with acute-onset right hemiparesis, following recovery from a diarrheal illness. Brain magnetic resonance imaging (MRI) revealed hyperintense signal changes involving the left globus pallidus. To the best of our knowledge, stroke mimic is a novel presentation in patients with SSADH deficiency.

## CASE REPORT

A 15-month-old girl, second born to third-degree consanguineously married parents from India, without apparent antenatal or neonatal risk factors, presented with a history of acute-onset paucity of movements in the right upper and lower

limbs. At the onset, she had multiple episodes of yellowish, watery stools mixed with mucus for 3 days. There was no history of vomiting or decreased urine output. On the 3<sup>rd</sup> day of illness, she had high-grade fever which was not associated with cough, cold, or ear discharge. The fever had subsided on the 4<sup>th</sup> day. She had sustained a trivial fall while playing on the 8<sup>th</sup> day and hit her head against the wall. There was no history of vomiting, bleeding, seizures, or loss of consciousness. Two days later, parents observed an acute-onset paucity of movements of the right upper and lower limbs. There was no history of vision or hearing disturbances, deviation of angle of the mouth, drooping of the eyelids, swallowing dysfunction, nasal twang, or nasal regurgitation. There was history of

**Address for correspondence:** Dr. Gautham Arunachal, Department of Human Genetics, National Institute of Mental Health and Neurosciences, Bengaluru - 560 029, Karnataka, India. Formerly, Assistant Professor, Department of Medical Genetics, Christian Medical College, Vellore - 632 004, Tamil Nadu, India. E-mail: gautham.arunachal@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

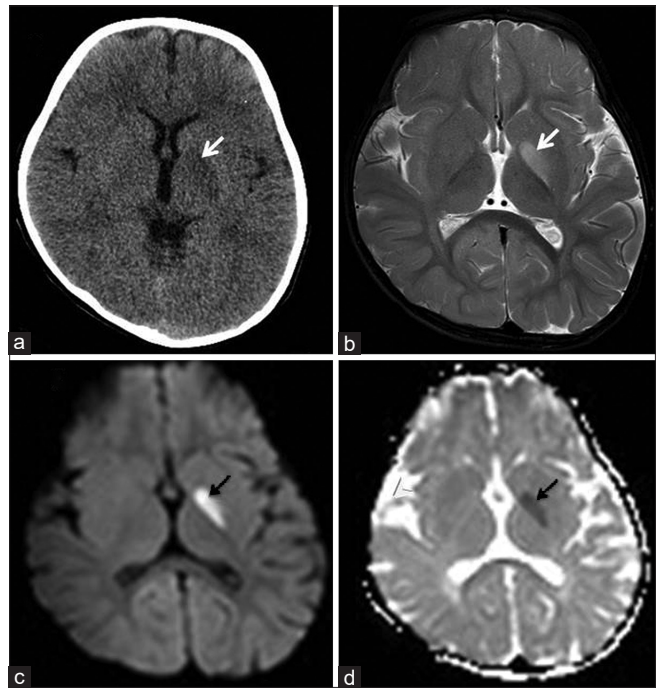
**DOI:** 10.4103/aian.AIAN\_213\_18

recurrent episodes of fast breathing in the past, and she was treated elsewhere with nebulization and oral antibiotics.

Premorbidly, the child could walk few steps with support, hold objects by pincer grasp, and she had stranger anxiety. She could not wave bye-bye, and there was no reciprocal babbling. There was only a poor response to name call, but her vision was normal. Apart from her mother, who had paralytic poliomyelitis in the childhood, her family history was noncontributory.

Anthropometry assessment at the time of presentation revealed a head circumference of 44.7 cm (3<sup>rd</sup> to 50<sup>th</sup> centile), weight of 10 kg (50<sup>th</sup> to 97<sup>th</sup> centile), and length of 80 cm (50<sup>th</sup> to 97<sup>th</sup> centile). Fleeting eye contact and fidgetiness were observed. She did not obey single-step commands and did not communicate her needs. She was not interested in her surroundings and displayed poor social interaction. Cranial nerve examination was normal. Tone was decreased in the right more than the left upper and lower limbs. Antigravity movements were preserved in the left side, while on the right side, she had only gravity eliminated movements. Deep tendon reflexes were diminished bilaterally. Bilateral plantar responses were extensor.

Initial possibilities considered were basal ganglia stroke following trivial trauma, demyelinating illness, or an organic aciduria such as methylmalonic acidemia or propionic acidemia. Stool enzyme-linked immunoassay was negative for rotavirus. Blood sugar and serum electrolytes were normal. Computerized tomography of the brain done in the acute phase [Figure 1a] showed hypodensity involving the left globus pallidus. MRI of the brain in the acute phase [Figure 1b-d] had revealed hyperintensity of the left globus pallidus on the T2-weighted axial image with restriction of diffusion in the left globus pallidus on the diffusion-weighted images. Electroencephalography (EEG) was normal. Visual evoked potential and brainstem auditory evoked responses were normal. Somatosensory-evoked potential of the tibial nerves had shown bilateral peripheral pathway dysfunction. Serum amino acid profile performed by high-performance liquid chromatography and acylcarnitine analyses performed by tandem mass spectrometry were normal. However, urine organic acid analysis performed by gas chromatography–mass spectrometry (GCMS) revealed increased excretion of 4-hydroxybutyric acid and threo- and erythro-4,5-dihydroxyhexanoic acid lactones, consistent with a diagnosis of SSADH deficiency (OMIM ID-#271980). This diagnosis was confirmed by the mutation analysis of *ALDH5A1*. Sanger sequencing of *ALDH5A1* revealed a homozygous variant, c.1343 + 1\_1343 + 3delGTainsTT, leading to a change in the consensus splice donor site of exon 8/intron 8 (Transcript ID ENST00000357578 with genomic coordinate Chr6: 24528395\_24528397 delGTainsTT; GRCh 37/hg19 build). Her parents were heterozygous for the same variant [Figure 2]. This variant is predicted to be pathogenic by various *in silico* prediction analysis tools and is previously reported as pathogenic in ClinVar database with submission accession SCV000268064.1 and allele ID-227703



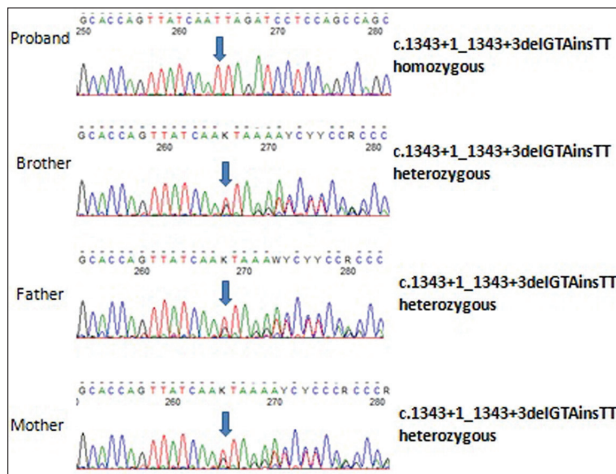
**Figure 1:** (a) Computed tomography brain showing hypodensity of the left globus pallidus (white arrow). (b) Magnetic resonance imaging brain: T2-weighted axial images showing hyperintensity of the left globus pallidus (white arrow). (c) Diffusion-weighted images showing hyperintensity in the left globus pallidus (black arrow) and (d) apparent diffusion coefficient images show low signal in the left globus pallidus (black arrow)

(The Single-Nucleotide Polymorphism Database [dbSNP] ID-875989801).

Once the diagnosis of SSADH deficiency was confirmed, treatment with vigabatrin in addition to the standard supportive measures was initiated. Follow-up assessment after 6 months revealed mild developmental gains. Hypotonia persisted, but the right hemiparesis had resolved. Follow-up imaging [Figure 3a-c] showed a near complete resolution of signal changes in the left globus pallidus and a subtle hyperintensity in the right globus pallidus on the T2-weighted axial image while the diffusion-weighted images were normal. Significant developmental gains were observed during a follow-up assessment after 2 years from the time of diagnosis.

## DISCUSSION

SSADH deficiency is a rare under-recognized disorder of GABA metabolism, although the exact incidence is not known. In our case, developmental delay, language deficit, hypotonia, hyporeflexia, and autistic traits were identified as described in the literature. To the best of our knowledge, this is the first report of a child with SSADH deficiency presenting as stroke mimic. The biochemical defect in SSADH deficiency is a failure to oxidize succinic semialdehyde to succinic acid. GABA transamination to succinic semialdehyde in the metabolic pathway is followed by its conversion to succinic

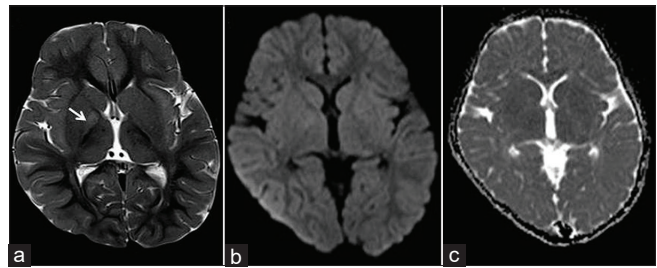


**Figure 2:** Electropherogram showing homozygous pathogenic variant, c.1343 + 1\_1343 + 3delGTainsTT, leading to a change in the consensus splice donor site of exon 8/intron 8 in proband. Parents and the unaffected sibling are heterozygous for the same variant

acid which enters the Krebs cycle.<sup>[2]</sup> However, in the absence of SSADH, succinic semialdehyde is reduced to 4-hydroxybutyric acid which is a neurotoxic agent.<sup>[2]</sup> Predominant right-sided weakness in our case could be explained by the asymmetric involvement of the basal ganglia.

Metabolic stroke has been reported in patients with homocystinuria, methylmalonic aciduria, glutaric aciduria Type I and II, isovaleric aciduria, propionic aciduria, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Fabry disease, and urea cycle disorders.<sup>[3,4]</sup> The exact pathophysiology of stroke in patients with SSADH is unclear. It is possible that 4-hydroxybutyric acid, a toxic metabolite that accumulates endogenously in children with SSADH deficiency, is neurotoxic as seen in our patient, leading onto the clinical manifestations. Although the exact reason behind such a presentation is unclear, we can derive an indirect explanation through the murine models of SSADH. It is postulated that hyperGABAergic state and elevated 4-hydroxybutyric acid affect neurotransmission and also cause escalation of various parameters of oxidative stress.<sup>[5]</sup> The catabolic process induced by infection as seen in our case might have worsened the underlying oxidative stress, followed by recovery with the cessation of the catabolic process.

Seizures are reported in nearly half of patients with SSADH deficiency, and various seizure semiology reported in these patients are generalized tonic-clonic seizures, absence seizures, partial and myoclonic seizures.<sup>[6]</sup> EEG abnormalities documented in patients with SSADH deficiency are background slowing, epileptiform discharges, electrical status epilepticus, asynchronous sleep spindles, and photosensitivity.<sup>[6,7]</sup> On the contrary, EEG may be normal in patients with SSADH deficiency.<sup>[6]</sup> Our patient had no seizures or electroencephalographic abnormalities. Dystonia, ataxia, and sleep disturbances were also absent in our patient.



**Figure 3:** (a) Magnetic resonance imaging brain: T2-weighted axial image at follow-up showing near complete resolution of signal changes in the left globus pallidus, while a subtle hyperintensity is seen in the right globus pallidus (white arrow). (b and c) Diffusion-weighted images and apparent diffusion coefficient images at follow-up are normal

Although hyporeflexia was documented in our case, nerve conduction parameters were normal for age.

Psychiatric symptoms described in patients with SSADH deficiency include sleep disorders, anxiety, pervasive developmental disorder, obsessive-compulsive disorder, hallucinations, aggression, and attention-deficit hyperactivity disorder.<sup>[8]</sup> Similarly, features of fleeting eye contact, fidgetiness, and lack of social interaction were observed in our case. Ocular manifestations such as strabismus, retinitis, nystagmus, and oculomotor apraxia have been described in patients with SSADH deficiency.<sup>[9]</sup> In contrast, no ocular manifestations were detected in our patient.

Blood tandem mass spectrometry was normal in our case, while urine GCMS had revealed increased excretion of 4-hydroxybutyric acid and threo- and erythro-4,5-dihydroxyhexanoic acid lactones, consistent with the diagnosis of SSADH deficiency. Our case emphasizes the importance and utility of urine GCMS in the diagnosis of metabolic disorders. The pathogenic variant detected in our case has likely been identified in at least three additional families, although the authors have used different nomenclature on at least two occasions. One author in the previous report used a mutation nomenclature with variants in two different nucleotide positions interspersed by a single wild-type allele (The two variants were c.1343 + 1delG and c.1343 + 3A>T with IDs in human gene mutation database: CD33523 and CS33487, respectively). It is unlikely that two variants coexisting independently with a wild type allele interspersed without any clear evidence of support.<sup>[10]</sup> It is our opinion that an “indel” is more plausible than two independent mutational events occurring *de novo* with blurring of the consequences of each event. The above-mentioned variant has been reported in ClinVar by a group from Persia with submission accession SCV000268064.1 and allele ID-227703 (dbSNP ID-rs875989801) with the indel nomenclature. Table 1 shows a comparison of the phenotype of our case and the two cases reported previously.

Brain MRI findings in patients with SSADH deficiency include normal imaging, delayed myelination, cerebral atrophy, cerebellar atrophy, and hyperintense signal changes involving bilateral globus pallidi, subthalamic nuclei, dentate nuclei,

**Table 1: Comparison of phenotype of our patient with previously reported patients with the same genotype**

Features	Proband in our report	Proband from Pakistan origin <sup>[1]</sup>	Proband from Palestinian–Lebanese origin <sup>[1]</sup>
Consanguinity	Yes (3 <sup>rd</sup> degree)	Yes (3 <sup>rd</sup> degree)	Yes (3 <sup>rd</sup> degree)
Age at presentation	15 months	42 months	4 months
Presenting symptom	Right hemiparesis	Generalized tonic-clonic seizures and encephalopathy	Hypotonia
Extrapyramidal symptoms	No	Choreoathetosis	No
Ataxia	No	Yes	No
Hypotonia	Yes	Normal tone at presentation Hypotonia at follow-up	Yes
Seizures	No	Yes	No
Natural course	Resolution of hemiparesis Hypotonia persists Developmental gains are observed on treatment	Resolution of encephalopathy and seizures Developmental gains and reduction in ataxia were observed on treatment	No data
Perinatal history	Uneventful	No data	No data
Neonatal and infantile period	Uneventful	Poor feeding and weak	No data
Family history	Nil	Present	Nil
Reflexes	Hyporeflexia	Normal	No data
Treatment response	Partial response	Treatment with vigabatrin was effective	No data
Neuroimaging	Asymmetrical hyperintensity of globus pallidi	Prominent subarachnoid spaces and large 4 <sup>th</sup> ventricle	No data
Enzyme activity	Not determined	Not determined	Not determined
EEG	Normal	Normal	No data

EEG: Electroencephalography

white matter, and brainstem involvement.<sup>[2,6]</sup> Although signal changes are symmetrical in patients with SSADH deficiency, asymmetrical or heterogeneous involvement does exist as seen in our patient.<sup>[11]</sup> Magnetic resonance spectroscopy may reveal elevated GABA and 4-hydroxybutyrate.<sup>[2,12]</sup> Therapeutic agents investigated in the management of SSADH deficiency are vigabatrin, taurine, NCS-382, SGS-742, and CGP-35348.<sup>[8]</sup> Vigabatrin may be used with an aim to reduce seizures and behavioral symptoms.<sup>[13]</sup> Magnesium valproate is also used in the management of epilepsy in patients with SSADH deficiency.<sup>[14]</sup> A pilot trial did not find a clinically significant improvement in the adaptive behaviour of patients with SSADH deficiency after treatment with taurine.<sup>[15]</sup> On treatment with vigabatrin, our patient had shown mild developmental gains at 6 months and significant developmental gains at 2 years of follow-up. Vigabatrin is an irreversible inhibitor of GABA transaminase, and variable clinical responses have been reported in patients with SSADH deficiency while on treatment with vigabatrin.<sup>[16]</sup>

Indistinct onset and course, the presence of altered sensorium or confusional state with or without the presence of involuntary movements, and focal seizures are the clinical clues for the diagnosis of metabolic stroke.<sup>[17,18]</sup> To summarize, metabolic stroke must be considered in children with developmental delay presenting with focal neurological deficits, coexistent seizures or altered sensorium, presence of multisystem involvement, positive family history, laboratory evidence of hypoglycaemia, dyselectrolytemia or acidosis, and involvement of highly

metabolically active sites in brain or areas of involvement not confined to an arterial territory on the neuroimaging.

## CONCLUSION

The phenotypic spectrum in patients with SSADH is widely expanding. Metabolic stroke may be a presenting symptom in children with SSADH deficiency. Children with developmental delay and stroke-like presentation should be evaluated with urine organic acid screening to exclude this disorder.

## Acknowledgment

We acknowledge Dr. Esther Andrew for helping in the clinical care of the patient.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Gibson KM, Christensen E, Jakobs C, Fowler B, Clarke MA, Hammersen G, *et al*. The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): Case reports of 23 new patients. *Pediatrics* 1997;99:567-74.
- Parviz M, Vogel K, Gibson KM, Pearl PL. Disorders of GABA metabolism: SSADH and GABA-transaminase deficiencies. *J Pediatr Epilepsy* 2014;3:217-27.
- Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 1: Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. *Arch Neurol* 2010;67:19-24.
- Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 2: Homocystinuria, organic acidurias, and urea cycle disorders. *Arch Neurol* 2010;67:148-53.
- Pearl PL, Parviz M, Vogel K, Schreiber J, Theodore WH, Gibson KM, *et al*. Inherited disorders of gamma-aminobutyric acid metabolism and advances in ALDH5A1 mutation identification. *Dev Med Child Neurol* 2015;57:611-7.
- Pearl PL, Hartka TR, Cabalza JL, Taylor J, Gibson MK. Inherited disorders of GABA metabolism. *Future Neurol* 2006;1:631-6.
- Pearl PL, Novotny EJ, Acosta MT, Jakobs C, Gibson KM. Succinic semialdehyde dehydrogenase deficiency in children and adults. *Ann Neurol* 2003;54 Suppl 6:S73-80.
- Kim KJ, Pearl PL, Jensen K, Snead OC, Malaspina P, Jakobs C, *et al*. Succinic semialdehyde dehydrogenase: Biochemical-molecular-clinical disease mechanisms, redox regulation, and functional significance. *Antioxid Redox Signal* 2011;15:691-718.
- Gordon N. Succinic semialdehyde dehydrogenase deficiency (SSADH) (4-hydroxybutyric aciduria, gamma-hydroxybutyric aciduria). *Eur J Paediatr Neurol* 2004;8:261-5.
- Liu N, Kong XD, Kan QC, Shi HR, Wu QH, Zhuo ZH, *et al*. Mutation analysis and prenatal diagnosis in a Chinese family with succinic semialdehyde dehydrogenase and a systematic review of the literature of reported ALDH5A1 mutations. *J Perinat Med* 2016;44:441-51.
- Pearl PL, Gibson KM, Quezado Z, Dustin I, Taylor J, Trzcinski S, *et al*. Decreased GABA-A binding on FMZ-PET in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2009;73:423-9.
- Ethofer T, Seeger U, Klose U, Erb M, Kardatzki B, Kraft E, *et al*. Proton MR spectroscopy in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2004;62:1016-8.
- Casarano M, Alessandri MG, Salomons GS, Moretti E, Jakobs C, Gibson KM, *et al*. Efficacy of vigabatrin intervention in a mild phenotypic expression of succinic semialdehyde dehydrogenase deficiency. *JIMD Rep* 2012;2:119-23.
- Vanadia E, Gibson KM, Pearl PL, Trapolino E, Mangano S, Vanadia F, *et al*. Therapeutic efficacy of magnesium valproate in succinic semialdehyde dehydrogenase deficiency. *JIMD Rep* 2013;8:133-7.
- Pearl PL, Schreiber J, Theodore WH, McCarter R, Barrios ES, Yu J, *et al*. Taurine trial in succinic semialdehyde dehydrogenase deficiency and elevated CNS GABA. *Neurology* 2014;82:940-4.
- Gropman A. Vigabatrin and newer interventions in succinic semialdehyde dehydrogenase deficiency. *Ann Neurol* 2003;54 Suppl 6:S66-72.
- Berkovic SF, Bladin PF, Darby DG. Metabolic disorders presenting as stroke. *Med J Aust* 1984;140:421-4.
- Sen S, Oppenheimer SM. Bedside assessment of stroke and stroke mimics. *Ann Indian Acad Neurol* 2008;11 Suppl S1:4-11.