

Succinic semialdehyde dehydrogenase deficiency (SSADH-D) in an eleven-month-old infant with marked hypotonia and staring episodes: a case report

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SUMMARY

Introduction. Succinic semialdehyde dehydrogenase deficiency (SSADH), also known as 4-hydroxybutyric aciduria (OMIM #271980, 610045), is an ultra-rare neurometabolic disorder inherited in an autosomal recessive pattern. It is usually characterised by a relatively nonprogressive encephalopathy in the first two years of life with hypotonia and developmental delay, associated with mild ataxia and hyporeflexia, as well as delays in language and speech development.

Case report. We report on a case of a four-year-old girl with SSADH deficiency who presented, at the age of 11 months old, with marked hypotonia, global neurodevelopmental delay and epilepsy. The diagnosis of "Succinic semialdehyde dehydrogenase deficiency" was indicated as there was a marked elevation of the levels of 4-hydroxy-butyr-ic and 3,4-dihydroxybutyric acid caused by mutation at the gene ALDH5A1 in the homozygous state, identified with WES technique. Currently, she is four years old and has a severe global psychomotor delay, excessive hypotonia, hyperextensibility, and ataxia and is free of seizures.

Conclusion. At the early stage of clinical presentation, the condition is difficult to differentiate from other encephalopathies. This case report suggests that analysis of urinary organic acids should be performed in all patients at risk to allow early diagnosis. DNA analysis with the WES technique can confirm the diagnosis.

Key words: SSADHD (Succinic semialdehyde dehydrogenase deficiency) • ALDH5A1 gene • GHB (γ-hydroxybutyric acid) • GABA (γ-aminobutyric acid)

INTRODUCTION

Succinic semialdehyde dehydrogenase deficiency (SSADH), also known as 4-hydroxybutyric aciduria (OMIM #271980, 610045), is an ultra-rare neurometa-

bolic disorder inherited in an autosomal recessive pattern. The incidence rate is unknown but estimated at 1:100000 (Malaspina et al., 2016; Wang et al., 2019).

Since the disorder was originally described in 1981, more than 450 cases of SSADH deficiency have been identified (Pearl et al., 2003). Due to the variability and nonspecific nature of associated symptoms, experts suggest that the disorder may be significantly underdiagnosed. (www.raredisease.com) In individuals with the disorder, the deficient activity of the SSADH enzyme disrupts the metabolism of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. SSADH deficiency leads to abnormal accumulation of the compound succinic semialdehyde, which is reduced or converted to 4-hydroxybutyric acid, also known as GHB (gamma-hydroxybutyric acid) within the cerebrospinal fluid, serum and urine. The urinary organic acid analysis is used to detect GHB and diagnose SSADH. GHB levels can increase to 2 and 800 times the normal level. The two diagnostic metabolites 3,4-dihydroxybutyric acid and 2,4-dihydroxybutyric are present in the organic acids' chromatogram (Menduti et al., 2018).

In individuals with SSADH deficiency, the range, severity, and presentation of specific symptoms and findings differ even among affected family members. SSADH deficiency leads to various and non-specific neurological clinical features. It is usually characterised by a relatively nonprogressive encephalopathy in the first two years of life with hypotonia and developmental delay, associated with mild ataxia and hyporeflexia (Pearl et al., 2011). Individuals with SSADH deficiency typically present with mild to severe global developmental delay and language and speech development delays in infancy and childhood. Hypotonia with hyporeflexia, nystagmus, hyperkinesia, ataxia, and choreoathetosis may also be present. Some affected individuals may also develop unusual irritability, easy agitation or frustration, increasingly aggressive behaviour, obsessive-compulsive disorder (OCD) or "autistic-like" behaviours. (www.raredisease.com) Non-progressive ataxia, behavioural problems and epileptic seizures can be seen in approximately 50% of the patients, while hypotonia and neuropsychiatric problems have occurred in 70% of patients. Eye symptoms such as strabismus, nystagmus, retinitis, optic disc paleness and oculomotor apraxia may also be detected (Pearl et al., 2003; www.raredisease.com). Sleep disorders are common and vary from excessive daytime somnolence to sleeping disorders, characterised by a reduction in REM sleep (Pearl et al., 2009).

The median age of diagnosis of SSADH deficiency is

two years, most cases being misdiagnosed. Nearly 80% of reported patients are diagnosed by the age of 5 years, although 10% of patients are diagnosed after the first decade (Lapalme-Remis et al., 2015).

We report on a case of a four-year-old girl with SSADH deficiency who presented, at the age of 11 months old, with marked hypotonia, global neurodevelopmental delay and epilepsy caused by mutation at the gene *ALDH5A1* in the homozygous state, identified with WES technique.

CASE PRESENTATION

An eleven-month-old female infant was referred to the neurology department due to hypotonia and delayed motor skills. She is the second child of non-consanguineous, Caucasian healthy parents, born full term after an uneventful pregnancy. Both antenatal and postnatal periods were uncomplicated. A week before her referral, the infant was hospitalised with Adenovirus gastrointestinal tract infection. In the last 24 hours, her parents reported minor episodes of gaze staring and excess salivation with awaking, lasting a few seconds.

On physical examination, there was no facial dysmorphism, only syndactyly of the 2nd and 3rd toes. Weight, height, and head circumference were in the 50th and 75th percentile. She had feeding difficulties and marked central hypotonia with minimal spontaneous movements against gravity. She could not fix and watch or attain a social smile. She was sitting with support, and she couldn't roll over.

Genetic analysis for SMA, Prader Willi and Rett syndrome was negative. Brain MRI revealed symmetrical hyperintensities of the globus pallidum on T2-weighted and FLAIR sequences mainly in the anterior part and delayed progress of the myelination regarding the patient's age (Figure 1). Interictal electroencephalogram (EEG) showed normal background activity with low voltage spikes (up to 150 μ V) arising mainly from the frontal area bilaterally. The patient then commenced treatment with carbamazepine (20 mg/kg/D) with a good response (Figure 2).

Metabolic screening (blood, urine, CSF) was performed. A Gas Chromatography-Mass Spectrometry (GC-MS) method was applied for the organic acids' identification and quantitation (G) method (Tanaka, 1980; Rinaldo, 2018). Concentrations were normalised to creatinine, and results were expressed as mmol/mol creatinine (Figure 3). The diagnosis of Succinic semialdehyde dehydrogenase deficiency was indicated as there

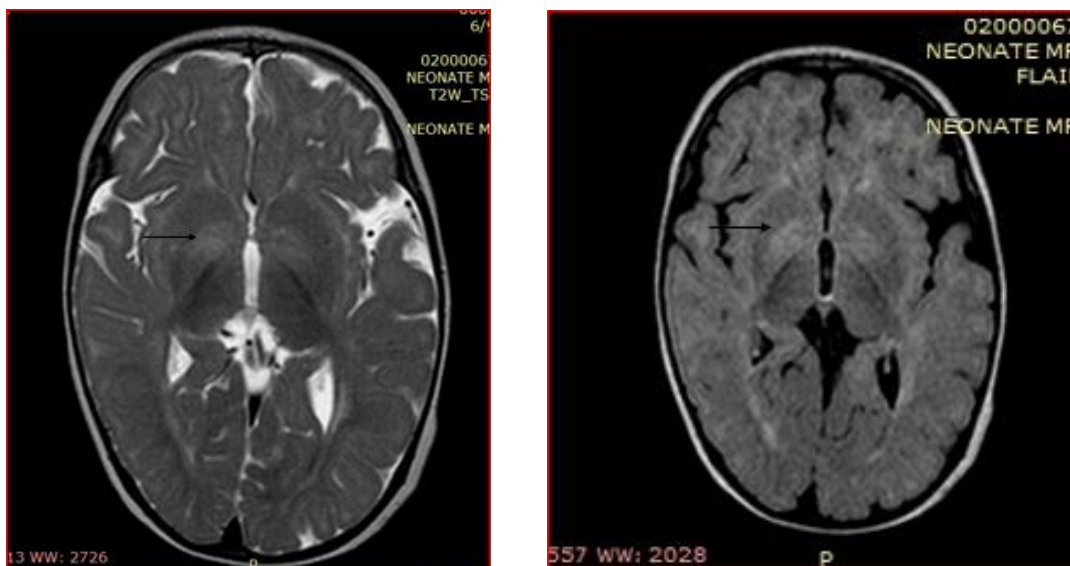


Figure 1. Magnetic resonance imaging of the brain. T2-weighted and FLAIR sequences with symmetrical hyperintensities of globus pallidi mainly in the anterior part (arrowhead) and delayed progress of the myelination with regards to the patient's age.

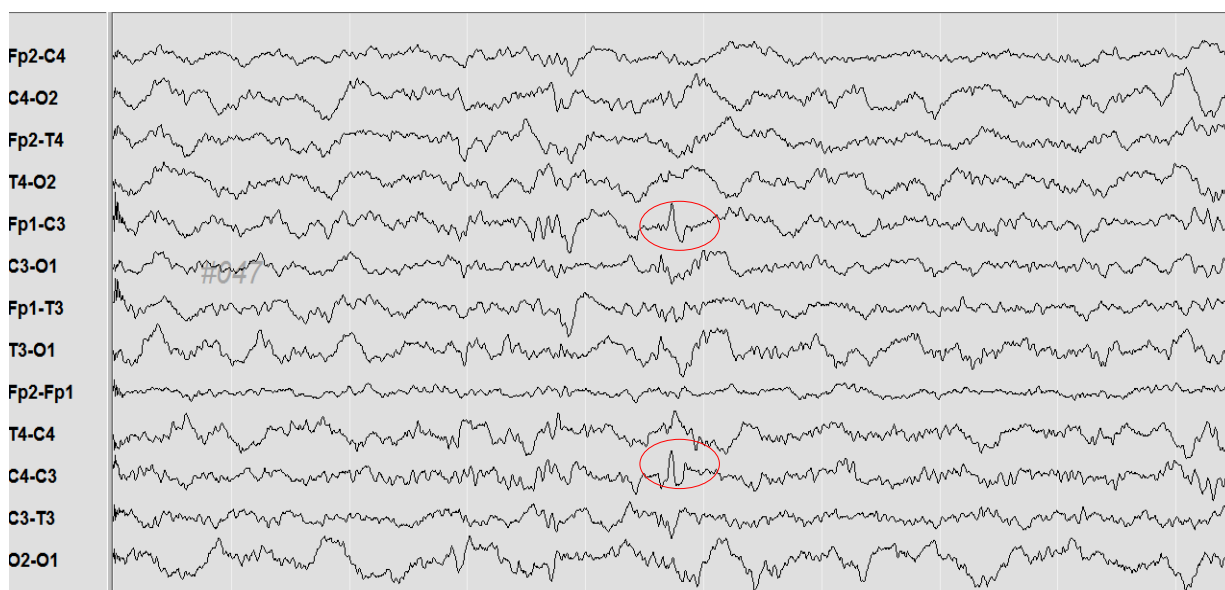


Figure 2. EEG at the age of diagnosis, showed low voltage spikes mainly in the frontal area.

was a marked elevation of the levels of 4-hydroxy-butyric acid (688.7 mmol/mol of urine Cr (normal values: 0) with co-existing high levels of 3,4-dihydroxybutyric acid and 2,4-dihydroxybutyric acid (values 180 and 30 mmol/mol creatinine, respectively). In addition, organic acids' analysis showed 5-fold and 7-fold increased values of the metabolites 2-hydroxy-glutaric acid and glutaric acid, which may also have harmful effects (Table 1).

The aminoacids' profile of the patient was also evaluated in both plasma and CSF (Mak et al., 2019). The analysis revealed normal values of all the amino acids tested, including the diagnostic metabolite glycine. The biogenic amines (neurotransmitters) and pterins in CSF were also determined according to the procedure described by Ormazabal et al. (2005). All the CSF metabolites tested (5-hydroxy-indoleacetic, homovanil-

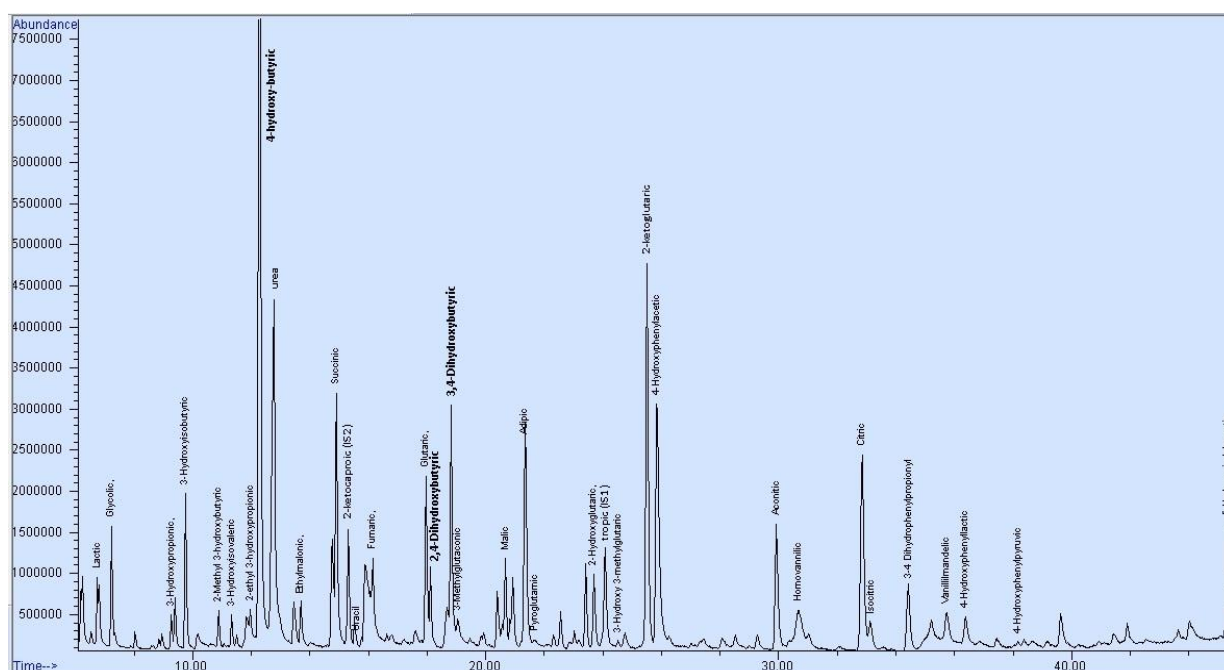


Figure 3. Chromatogram of urine organic acids of the patient with SSADH, by Gas Chromatography-Mass Spectrometry. The presence of the diagnostic metabolites 4-hydroxy-butyric, 3,4-dihydroxybutyric acid and 2,4-dihydroxybutyric acid confirm the characteristic pattern of the disease.

Table 1. Values of the metabolites of the child with SSADH. Pathological values are shown in bold

Metabolite	Biological fluid/analysis	Value	Reference value
4-hydroxy-butyric	Urine/Organic acids	688.7 mmol/mol creatinine	n.d. ¹
3,4- dihydroxybutyric	Urine/Organic acids	180 mmol/mol creatinine	n.d. ¹
2,4- dihydroxybutyric	Urine/Organic acids	30 mmol/mol creatinine	n.d. ¹
3-hydroxy-propionic	Urine/Organic acids	149.4 mmol/mol creatinine	1.0–36.0 mmol/mol creatinine
2-hydroxy-glutaric ²	Urine/Organic acids	76.8 mmol/mol creatinine	0.0–15.0 mmol/mol creatinine
glutaric ²	Urine/Organic acids	36.2 mmol/mol creatinine	0.0–5.3 mmol/mol creatinine
glycine	Plasma/Aminoacids	289.0 μmol/L	107.0–343 μmol/L
	CSF/Aminoacids	4.0 μmol/L	3.7–7.6 μmol/L
5-hydroxy-indoleacetic	CSF/ Biogenic amines	184.0 nmol/L	170.0–490.0 nmol/L
homovanillic	CSF/ Biogenic amines	630.0 nmol/L	344.0–906.0 nmol/L
3-ortho-methyldopa	CSF/ Biogenic amines	20.0 nmol/L	4.0–50.0 nmol/L
5-hydroxy-tryptophan	CSF/ Biogenic amines	7.0 nmol/L	1.6–15.0 nmol/L
neopterin	CSF/ Pterins	31.0	8.0–43.0 nmol/L
biopterin	CSF/ Pterins	41.0	8.0–54.0 nmol/L

¹ (n.d.) – not detected; ² – metabolite potential harmful, but not diagnostic for SSADH

lic, 3-ortho-methyldopa, 5-hydroxy-tryptophan, neopterin, biopterin) were found within the normal range, as expected.

Whole exome sequencing was performed in an Illumina HiSeq 2000 sequencer (100 bp paired-end, Illumina, San Diego, CA, USA), and the hg19 (GRCh37) assembly was used as a reference genome. A single ho-

mozygous missense pathogenic variant on the exon 8 of the gene ALDH5A1 (c.1226G>A; p.Gly409Asp, NM_001080.3) was identified, which confirmed the diagnosis of succinic semialdehyde dehydrogenase deficiency. The ALDH5A1 gene encodes for the succinic semialdehyde dehydrogenase involved in the catabolism of GABA (Chambliss et al., 1995). Pathogen-

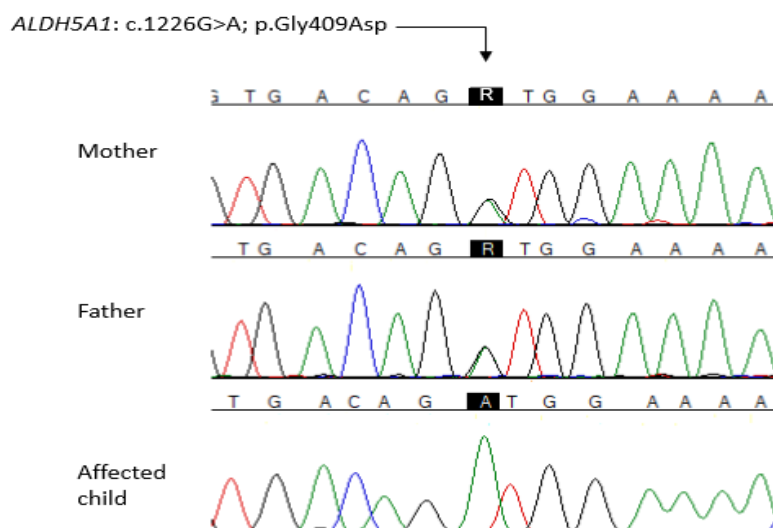


Figure 4. Electropherograms depicting the parental heterozygosity as well as the patient's homozygosity for the pathogenic variant.

ic variants of the *ALDH5A1* gene are known to cause deficiency of the mitochondrial SSADH (Akaboshi et al., 2003). The mutation was validated by bidirectional Sanger sequencing on an ABI 3500xL (Life Technologies, Carlsbad, CA). Subsequent Sanger sequencing of parental samples confirmed that both parents were carriers for the same mutation (Figure 4). Genetic counselling was offered to the family regarding recurrence risk and reproductive options. Specifically, the family was informed that due to the autosomal recessive mode of inheritance, there is a recurrence risk of 25%. The couple was offered the choice of preimplantation genetic test and prenatal diagnosis (by chorionic villus sampling or amniocentesis). Additionally, the possibility of carrier testing was provided to other family members.

At 2 ½ years old, at regular follow-up, she could not sit without support and had a severe speech delay. She was free of seizures and still on antiepileptic treatment (carbamazepine). Her interictal sleep EEG revealed a different pattern than the first EEG, with intermittent rhythmic delta activity (1–2 Hz, up to 250 µV) mainly in the bilateral parietal-occipital area (Figure 5).

At the recent re-evaluation at four years old, weight, height and head circumference were all at the 50th percentile. She still has a severe global psychomotor delay and has not attained speech. She presents with excessive hypotonia and hyperextensibility, especially in the lower limbs. Gait instability and ataxia, mainly in the trunk and insufficient voluntary use of hands are also

notable. She can sit without support; she can walk independently with frequent falls. She has right eye strabismus with good eye contact. Her parents report no sleep problems. She is still on antiepileptic treatment with carbamazepine (20 mg/kg/D), and she has been free of seizures since the commencement of the treatment. Her interictal sleep EEG shows low voltage spikes mainly in the frontal-temporal area bilaterally (shown in Figure 6). Brain MRI shows no significant change. She follows speech, physical, and occupational therapy on a weekly schedule. The couple decided to proceed to a third child by natural conception. Prenatal diagnosis by chorionic villus sampling revealed that the embryo was heterozygous for the p.Gly409Asp pathogenic variant; thus, a healthy boy was born a few months later.

DISCUSSION

The patient in our report was diagnosed at 11 months old. Excessive hypotonia with hyporeflexia, delay of acquired infantile milestones, and staring episodes were the reasons for neurology assessment. The clinical manifestations of our patient are consistent with the signs and symptoms of neurometabolic disorder. GHB and 4,5DHHA in the urinary organic acid analysis were dramatically elevated, and brain MRI findings were typical of the disorder. The WES technique identified a homozygous mutation on the *ALDH5A1* gene, confirming the diagnosis of SSADH deficiency.

The gene responsible for SSADH deficiency is lo-

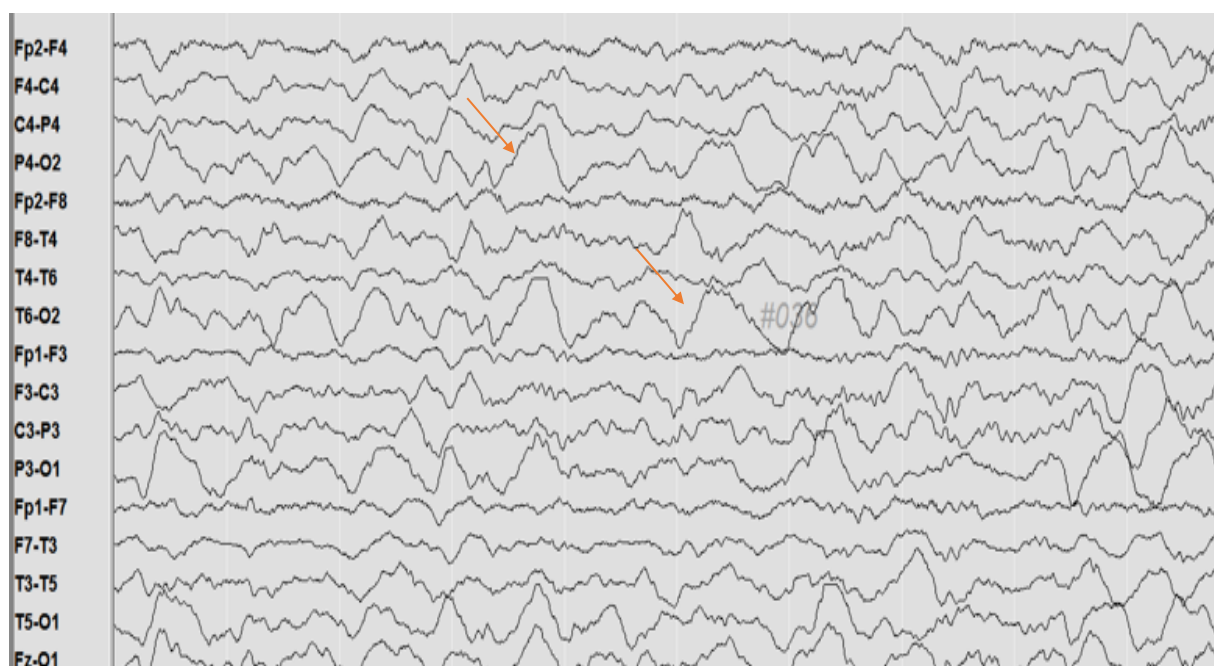


Figure 5. Interictal sleep EEG at the age of 2 ½ years old, with intermittent rhythmic delta activity (1–2Hz, up to 250 µV) mainly in parietal-occipital area bilaterally.

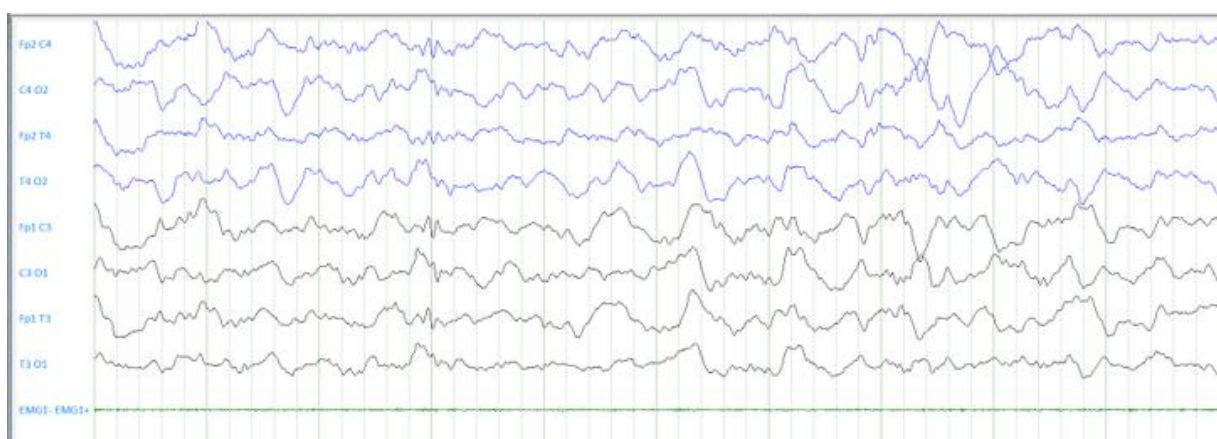


Figure 6. Interictal sleep EEG, at the age of 4 years old, shows low voltage spikes mainly in frontal-temporal area bilaterally.

cated on the short arm of chromosome 6 (6p22.3), comprises ten exons and produces an open reading frame of 535 amino acids. More than 60 mutations of ALDH5A1 have been identified and are considered the leading cause of decreasing or eliminating SSADH activity (Brennenstuhl et al., 2020). The spectrum of disease-causing mutations consists of frameshift, non-sense, splice mutations and larger deletions. However, most mutations are missense (Akaboshi et al., 2003). The c.1226G>A; p.Gly409Asp leading to substitution of aspartic acid for glycine at position 409 (G409D)

of the polypeptide sequence, lies on the catalytic domain of the enzyme and has been found to cause a loss of enzyme activity of almost 100% (Akaboshi et al., 2003; Lemes et al., 2006). This mutation has been previously reported in families with different geographic origins (Leo et al., 2017), including Greece (Akaboshi et al., 2003; Hogema et al., 2001; Attri et al., 2017) and affects a highly conserved amino acid. However, the phenotype-genotype relation was not completely understood. Akaboshi et al. (2003) suggested that residual enzyme expression is not likely to be an essential

factor contributing to the substantial phenotypic differences observed among different families and even among sibs, implying that other modifying factors are of great importance in disease pathology.

Epilepsy is present in approximately half of affected individuals (Pearl et al., 2011). The infantile onset of epilepsy is less typical but does occur, as in our patient. Epilepsy often appears later in childhood or adolescence and is more prevalent in adults than in pediatric cohorts (Lapalme-Remis et al., 2015). The severity of epilepsy ranges from a mild impairment, with some patients having sporadic or recurrent episodes, to the progressive neurodegenerative course with intractable seizures in infancy or even generalised convulsive status epilepticus (Lapalme-Remis et al., 2015). Epileptiform discharges on EEG tend to be generalised and sometimes multifocal, but focal spikes may also be present (Pearl et al., 2009). In our patient's EEGs, we can see a different pattern, probably showing the progress of the disease. Photosensitivity discharge, background slowing and sleep spindle asynchrony have also been described (Pearl et al., 2003; Pearl et al., 2011).

A broad spectrum of antiepileptic medications has been used in patients with SSADH-D. As in our patient, sodium channel blockers lamotrigine and carbamazepine seem to be the most helpful. Since Valproic acid may reduce residual SSADH enzyme activity, it is contraindicated, but it may sometimes be considered in cases with refractory seizures. Vigabatrin, an irreversible inhibitor of GABA transaminase, aims to reduce GHB's high concentrations by preventing GABA's conversion to SSA. Clinical efficiency of vigabatrin is restricted as it can cause narrowing of the visual field, and there are no randomised controlled studies (Pearl et al., 2003; Didiasova et al., 2020).

There is no optimal treatment for SSADH deficiency. The treatment is symptomatic and supportive, directed towards the specific symptoms that are apparent in each individual. Methylphenidate, thioridazine, risperidone and fluoxetine have been helpful in some patients for psychiatric symptoms (Pearl et al., 2009). Clonidine has been used to improve REM sleep. Early intervention may ensure that children with SSADH deficiency reach their potential.

CONCLUSION

Herein we present a case of a child with an ultra-rare neurometabolic disorder such as SSADH-D. At the early stage of clinical presentation, the condition is diffi-

cult to differentiate from other encephalopathies. This case report suggests that analysis of urinary organic acids should be performed in all patients at risk to allow early diagnosis. If there are also hyperintensive changes in globus pallidus in brain MRI, SSADH deficiency should be considered. Gene mutation analysis can contribute to the diagnosis of SSADH deficiency in clinical practice and the screening of ALDH5A1 gene mutation carriers, allowing the patients' families to have a healthy child, as in our case.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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