Natural history of succinic semialdehyde dehydrogenase deficiency through adulthood

Samuel Lapalme-Remis,
MDCM, MA
Evan Cole Lewis, MD
Christine De
Meulemeester, MD
Pranesh Chakraborty,
MD
K. Michael Gibson, PhD
Carlos Torres, MD
Alan Guberman, MD
Gajja S. Salomons, PhD
Cornelis Jakobs, PhD
Andre Ali-Ridha, MD
Mahsa Parviz, BS
Phillip L. Pearl, MD

Correspondence to
Dr. Lapalme-Remis:
lapalmeremis@gmail.com

ABSTRACT

Objective: The natural history of succinic semialdehyde dehydrogenase (SSADH) deficiency in adulthood is unknown; we elucidate the clinical manifestations of the disease later in life.

Methods: A 63-year-old man with long-standing intellectual disability was diagnosed with SSADH deficiency following hospitalization for progressive decline, escalating seizures, and prolonged periods of altered consciousness. We present a detailed review of his clinical course and reviewed our SSADH deficiency database adult cohort to derive natural history information.

Results: Of 95 patients in the database for whom age at diagnosis is recorded, there are 40 individuals currently aged 18 years or older. Only 3 patients were diagnosed after age 18 years. Of 25 adults for whom data are available after age 18, 60% have a history of epilepsy. Predominant seizure types are generalized tonic-clonic, absence, and myoclonic. EEGs showed background slowing or generalized epileptiform discharges in two-thirds of adults for whom EEG data were collected. History of psychiatric symptoms was prominent, with frequent anxiety, sleep disturbances, and obsessive-compulsive disorder.

Conclusions: We identified patients older than 18 years with SSADH deficiency in our database following identification and review of a patient diagnosed in the seventh decade of life. The illness had a progressive course with escalating seizures in the index case, with fatality at age 63. Diagnosis in adulthood is rare. Epilepsy is more common in the adult than the pediatric SSADH deficiency cohort; neuropsychiatric morbidity remains prominent. *Neurology*® 2015;85:861-865

GLOSSARY

GHB = γ -hydroxybutyric acid; **SSADH** = succinic semialdehyde dehydrogenase; **SUDEP** = sudden unexplained death in epilepsy.

Succinic semialdehyde dehydrogenase (SSADH) deficiency, an autosomal recessive inborn error of γ -aminobutyric acid metabolism, leads to accumulation of γ -hydroxybutyric acid (GHB), enabling detection via urinary organic acid testing.^{1,2}

Approximately 450 patients have been identified,³ with a typical phenotype of developmental delay starting in late infancy and a subsequent nonprogressive encephalopathy with cognitive deficiency, expressive language impairment, ataxia, and epilepsy.⁴ Severity ranges from mild impairment⁵ to a relentlessly progressive neurodegenerative course with intractable seizures in infancy.⁶ MRI shows a dentatopallidoluysian pattern. EEG frequently shows background slowing and generalized epileptiform abnormalities.

Given the nonspecific symptoms and wide phenotypic expression, undiagnosed cases are likely. The mean age at diagnosis is 2 years, and few adult patients are reported.³ We report a patient diagnosed with SSADH deficiency at age 63 and review our cohort of adult patients.

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From the Division of Neurology, Department of Medicine (S.L.-R., C.D.M., A.G.) and Department of Radiology (C.T.), The Ottawa Hospital, University of Ottawa, Ottawa, Canada; Division of Neurology (E.C.L.) and Department of Pediatrics (P.C.), Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario, Canada; Division of Experimental and Systems Pharmacology (K.M.G.), Washington State University College of Pharmacy, Spokane, WA; Department of Clinical Chemistry (G.S.S., C.J.), Metabolic Unit, Polikliniek rec. K (PK 1X 009), VU University Medical Center, Amsterdam, the Netherlands; University of Ottawa Eye Institute (A.A.-R.), Ottawa, Ontario, Canada; and Department of Epilepsy & Clinical Neurophysiology (M.P., P.L.P.), Harvard Medical School, Boston Children's Hospital, Boston, MA. Dr. Lapalme-Remis is currently with the Mayo Clinic, Rochester, MN. Dr. Lewis is currently with The Hospital for Sick Children, Toronto, Ontario, Canada. Dr. Ali-Ridha is currently with McGill University, Montreal, Quebec, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

METHODS An adult man with a long-standing history of intellectual disability and seizures was diagnosed with SSADH deficiency at age 63 years following hospitalization. Subsequently, we reviewed our SSADH database, acquired as a cross-sectional study, for characteristics of patients older than 18 years. The database is taken from a registry of patients with SSADH deficiency initiated in 2001 for whom at least a single completed questionnaire was submitted by the patient's family or referring physician. The database is periodically updated upon receipt of follow-up data. Diagnosis is confirmed by a clinical history consistent with SSADH deficiency and one or more of the following laboratory criteria: enzymatic quantification study, *ALDH5A1* gene sequencing, or persistent γ -hydroxybutyric aciduria without exogenous GHB.

Standard protocol approvals, registrations, and patient consents. The Boston Children's Hospital Institutional Review Board approved this study.

CASE REPORT The index case was born to nonconsanguineous parents. Family history was notable for a deceased sister with precocious puberty, developmental delay, and seizures.

The patient had global developmental delay from late infancy. He was late to walk, and speech onset occurred at age 4. Motor skills were impaired but he learned to ride a bicycle in adolescence and acquired rudimentary reading, writing, and arithmetic by early adulthood.

He found employment in a sheltered workshop and later worked as a custodian. He was described as talkative, sociable, and obsessed with routines, orderliness, and cleanliness. He was prone to anxiety, hoarding, and daytime drowsiness.

At age 15 he had an unwitnessed fall followed by confusion, and at age 19 he had a witnessed generalized tonic-clonic seizure. Phenytoin was initiated. He continued to have seizures approximately every 2.5 years from ages 19 to 46.

At age 46 he experienced a cluster of generalized tonic-clonic seizures and episodes of altered consciousness characterized by slow responses, decreased verbal output, and a fine motor tremor, sometimes terminating in a generalized tonic-clonic

Figure 1 MRI images

Brain MRI images of a patient with succinic semialdehyde dehydrogenase deficiency at age 62. (A) Axial T2-weighted image showing increased T2 signal intensity in the bilateral dentate nuclei of the cerebellum (arrows). (B, C) Axial T2-weighted sequences showing increased signal intensity of the bilateral globi pallidi (arrows in B and dotted lines in C). Of note, there are dilated perivascular spaces and chronic lacunes in both basal ganglia, left greater than right. (D) Axial fluid-attenuated inversion recovery (FLAIR) sequence showing parenchymal volume loss more than expected for age.

Figure 2 Distribution of current age or age at death and age at diagnosis of patients in SSADH deficiency database (n = 95)

Age distribution of patients in the succinic semialdehyde dehydrogenase (SSADH) deficiency database at time of diagnosis and in February 2015 or at time of death.

seizure. Neurologic examination revealed horizontal nystagmus and mixed resting and action tremor. Basic laboratory screening, including electrolytes, renal function, and hepatic function, was normal except for a mildly elevated ammonia level of 41 $\mu\text{mol/L}$. Head CT showed hypodensities in the basal ganglia. EEG showed diffuse background slowing with sharp and slow waves. Shortly following an increase in phenytoin dosage and addition of clobazam, seizure frequency returned to near baseline over the next 9 years. Symptoms of anxiety, poor sleep, and excessive daytime somnolence persisted.

At age 55 he again displayed repeated episodic disorientation, drowsiness, tremor, and increased frequency of generalized tonic-clonic seizures, followed by a stepwise progressive decline over the remaining

years of his life. During this period he exhibited clustering of seizures and was never seizure-free for more than a few months.

His final admission to hospital was at age 62 for episodes of altered level of consciousness leading to inability to self-care. Based on elevated serum ammonia values (peak 68 $\mu\text{mol/L}$), metabolic investigations were undertaken and revealed markedly increased urinary GHB (285 mmol/mol creatinine) and 3,4 dihydrobutyric acid (620 mmol/mol creatinine). Enzymatic assay of lymphocytes revealed absent SSADH. *ALDH5A1* sequencing revealed compound heterozygosity for 2 previously described mutations: c.1015-2A>C (mutation of canonical splice-site) and c.608C>G; p.(Pro203Arg). His mother was identified as heterozygous for c.1015-2A>C mutation, consistent with mutations in trans. Paternal DNA was not available.

During admission the patient exhibited frequent generalized tonic-clonic seizures with prolonged and progressively lengthening periods of obtundation separated by occasional alertness; interictal EEGs did not confirm nonconvulsive status epilepticus. MRI (figure 1) demonstrated parenchymal volume loss and increased signal intensity within the dentate nuclei and globus pallidi.

Trials of vigabatrin and levetiracetam did not produce improvement. The patient died at age 63 following months of persistent obtundation. No autopsy was performed.

ADULT COHORT RESULTS Of 112 patients in the SSADH deficiency database, 95 have a documented age at diagnosis. Of these, there is a cohort of 40 individuals aged 18 years and older as of February 2015; we have received clinical data from the adult years for 25 of these individuals. The current age stratification is 31 patients ages 18–29 years, 7 patients ages 30–39 (including 1 deceased), 1 patient age 46, and the reported patient, deceased at age 63. Only 3 patients were diagnosed after age 18 years (figure 2).

Among patients for whom data were obtained after age 18, 15 adult patients (60%) have a history of epilepsy compared with 45 (47%) of the total patient population ($p < 0.01$), with generalized tonic-clonic, absence, and myoclonic seizures predominating (table). Of 15 patients with EEG data, 5 (33%) were normal, 5 (33%) had background slowing or disorganization, and 5 (33%) had generalized interictal spike-wave discharges. Neuropsychiatric symptoms are listed in the table.

DISCUSSION Given the recent discovery of SSADH deficiency and its usual diagnosis at an early age, there is limited information on its natural history in

Table Clinical features of adult patients with succinic semialdehyde dehydrogenase deficiency (n = 25)

Epilepsy	15 (60)
Generalized tonic-clonic seizures	11 (44)
Absence seizures	7 (28)
Myoclonic seizures	5 (20)
Focal-onset seizures	5 (20)
Anxiety	13 (52)
Obsessive-compulsive behaviors	12 (48)
Hyperactivity	12 (48)
Sleep disturbance	14 (56)

Data are n (%).

adulthood. The case report underscores the challenges in identification of this variable disease.

Early in life his presentation was typical, with moderate developmental impairment and infrequent generalized tonic-clonic seizures. As he reached late middle age, his phenotype was characterized by clustering of seizures and a gradual and progressive encephalopathy resulting in functional decline and death. Evidence for chronic oxidative stress associated with neuronal degeneration and apoptosis in the murine model suggests a possible explanation for the adult course.⁷

Our database analysis suggests that SSADH deficiency is rarely diagnosed in adulthood. Epilepsy is present in a higher proportion than in the pediatric population, possibly suggesting progressive hyperexcitability in the disorder.

One other adult database patient died at age 33. Death was consistent with sudden unexplained death in epilepsy (SUDEP) in the context of worsening seizure control. In addition, we know of 2 other adult SSADH patient deaths not included in the database. Both were consistent with SUDEP: one occurred in a woman aged 19 who was diagnosed posthumously and whose neuropathology was later published⁸ and the other occurred in a man in his mid-20s (oral communication, K.M.G. and P.L.P., 2015).

A limitation of the study is the nonuniform data collection and cross-sectional nature of the database analysis. We derived nondemographic clinical data on the adult population from only those patients whose most recent data were obtained after age 18. As with all cross-sectional analyses, we cannot draw conclusions about disease progression over time.

This study highlights the importance of considering inherited inborn errors of metabolism and other genetic and childhood-onset pathologies in adults with long-standing developmental delay or seizures.⁹ Even when previously investigated, many patients presented before entities such as SSADH deficiency were discovered, or testing may have been unavailable or inaccurate. Physicians who see them later in life should consider genetic-metabolic conditions. We expect that adults with childhood onset of symptoms without previous genetic-metabolic testing have a similar diagnostic yield as that described in the pediatric population.¹⁰

AUTHOR CONTRIBUTIONS

Samuel Lapalme-Remis contributed to the care and diagnosis of the case report patient, acquisition of clinical data, conception of the manuscript, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. Evan Cole Lewis contributed to the care and diagnosis of the case report patient, acquisition of clinical data, conception of the manuscript, critical review of the manuscript, and final approval of the version to be published. Christine De Meulemeester contributed to the care and diagnosis of the case report patient, acquisition of clinical data, critical review of the manuscript, and final approval

of the version to be published. Pranesh Chakraborty contributed to the conception of the manuscript, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. K. Michael Gibson contributed to the conception of the manuscript, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. Carlos Torres contributed to the acquisition and interpretation of imaging data for the case report, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. Alan Guberman contributed to the care and diagnosis of the case report patient, acquisition of clinical data, critical review of the manuscript, and final approval of the version to be published. Gajja S. Salomons contributed to the diagnosis of the case report patient, acquisition of clinical data, critical review of the manuscript, and final approval of the version to be published. Cornelis Jakobs contributed to the diagnosis of the case report patient, acquisition of clinical data, critical review of the manuscript, and final approval of the version to be published. Andre Ali-Ridha contributed to the acquisition of clinical data, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. Mahsa Parviz contributed to the acquisition and analysis of the SSADH deficiency database data, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. Phillip L. Pearl contributed to the acquisition and analysis of the SSADH deficiency database data, conception of the manuscript, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published.

ACKNOWLEDGMENT

The authors are grateful for the assistance and support of the family of the index patient described in this report. Dr. Lapalme-Remis thanks his late father, Dr. Robert S. Remis, for his helpful criticism and advice regarding an early draft of this manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received August 11, 2014. Accepted in final form March 20, 2015.

REFERENCES

1. Gibson KM, Sweetman L, Nyhan WL, et al. Succinic semialdehyde dehydrogenase deficiency: an inborn error of gamma-aminobutyric acid metabolism. *Clin Chim Acta* 1983;133:33–42.
2. Pearl PL, Taylor JL, Trzcinski S, Sokohl A. The pediatric neurotransmitter disorders. *J Child Neurol* 2007;22:606–616.
3. Pearl PL, Shukla L, Theodore WH, Jakobs C, Gibson KM. Epilepsy in succinic semialdehyde dehydrogenase deficiency, a disorder of GABA metabolism. *Brain Dev* 2011;33:796–805.
4. Pearl PL, Novotny EJ, Acosta MT, Jakobs C, Gibson KM. Succinic semialdehyde dehydrogenase deficiency in children and adults. *Ann Neurol* 2003;54:S73–S80.
5. Gibson KM, Christensen E, Jakobs C, et al. The clinical phenotype of succinic semialdehyde dehydrogenase deficiency (4-hydroxybutyric aciduria): case reports of 23 new patients. *Pediatrics* 1997;99:567–574.
6. Yamakawa Y, Nakazawa T, Ishida A, et al. A boy with a severe phenotype of succinic semialdehyde dehydrogenase deficiency. *Brain Dev* 2012;34:107–112.
7. Latini A, Scussiato K, Leipnitz G, Gibson KM, Wajner M. Evidence for oxidative stress in tissues derived from succinate semialdehyde dehydrogenase-deficient mice. *J Inher Metab Dis* 2007;30:800–810.

8. Knerr I, Gibson KM, Murdoch G, et al. Neuropathology in succinic semialdehyde dehydrogenase deficiency. *Pediatr Neurol* 2010;42:255–258.
9. Sedel F, Gourfinkel-An I, Lyon-Caen O, Baulac M, Saudubray JM, Navarro V. Epilepsy and inborn errors of metabolism in adults: a diagnostic approach. *J Inher Metab Dis* 2007;30:846–854.
10. Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2011; 77:1629–1635.

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