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RESEARCH REPORT

Incidence and Geographic Distribution of Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency

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Abstract The incidence of succinic semialdehyde dehydrogenase (SSADH) deficiency, an autosomal recessive inherited disorder of GABA degradation, is unknown. Upon a recent diagnosis of a new family of affected fraternal twins from the Punjabi ethnic group of India, case ascertainment from the literature and our database was done to determine the number of confirmed cases along with their geographic distribution. The probands presented with global developmental delay, infantile onset epilepsy, and a persistent neurodevelopmental disorder upon diagnosis at 10 years of age with intellectual disability, expressive aphasia, and behavioral problems most prominent for hyperactivity. Gamma-hydroxybutyric aciduria and homozygous ALDH5A1 c.608C>T; p.Pro203Leu mutations were confirmed. Identification of all available individual cases with clinical details available including geographic or ethnic origin revealed 182 patients from 40 countries, with the largest number of patients reported from the USA (24%), Turkey (10%), China (7%), Saudi Arabia (6%), and Germany (5%). This study provides an accounting of all published cases of confirmed SSADH deficiency and provides data useful in planning further studies of this rare inborn error of metabolism.

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Summary Statement: This study provides the worldwide geographic distribution of SSADH deficiency from all identified published cases and subjects in the investigators' database.

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Introduction

Succinic semialdehyde dehydrogenase (SSADH) deficiency (OMIM 271980, 610045) is a rare autosomal recessive disorder of GABA degradation initially described in 1981 (Jakobs et al. 1981). GABA-transaminase (GABA-T) converts GABA to succinic semialdehyde, which is metabolized to succinic acid by SSADH. In SSADH deficiency, there is an excessive buildup of GABA and γ-hydroxybutyrate (GHB). High levels of GABA and GHB have been implicated in the neurological manifestations of SSADH deficiency, and recent evidence suggests multiple metabolic perturbations may be associated with the pathophysiology including markers of oxidative stress, dysregulation of autophagy including the mTOR pathway, and accumulation of the semialdehyde intermediate.

SSADH deficiency does not typically feature intermittent deterioration or neurodevelopmental regression and may be relegated to a nonprogressive encephalopathy or atypical neurobehavioral syndrome with either a missed diagnosis or identification late into adulthood (Lapalme-Remis et al. 2015). We report affected twins from the second family reported from India and the first since the early report of three affected siblings from 1997 that added

23 new cases to the literature and described the phenotype (Gibson et al. 1997). We subsequently reviewed the literature to identify all reported cases since the initial description of urinary gamma-hydroxybutyric aciduria (Jakobs et al. 1981) and added patients from our database with a confirmed diagnosis.

Methods

Clinical and genetic confirmation of SSADH deficiency of a Punjabi family from Northern India came to our attention as the second affected family reported from India and the first in 20 years. We reviewed the literature and our database for confirmed cases of SSADH deficiency and report on the geographic origin of reported patients. Collection and reporting of subjects from our database was approved by the Boston Children's Hospital Institutional Review Board.

Case Reports and Results

Ten-year-old dizygotic twin boys born to a North Indian couple of the Punjabi ethnic group presented for evaluation of developmental disability and a history of seizures. There was no known history of consanguinity or family history of neurodevelopmental disorders.

Twin A presented with cognitive impairment, profound deficit of expressive language, and incoordination. Behavior was notable for hyperactivity and, at times, aggressiveness. Developmental assessment indicated moderate intellectual deficiency with WISC-III Full Scale IQ measurement of 43, gross motor skill level approximating age 4 years, and fine motor skills at 14 months. Activities of daily living were affected such that the patient could not dress independently or drink from a cup without spillage. The proband had onset of convulsive seizures at 3 months of age. Delayed developmental with hypotonia was noted then. The past medical history disclosed no gestational or perinatal problems, but acquisition of developmental milestones was notable for head control at 12 months, independent sitting 30 months, independent standing at 36 months, and walking at 42 months. On neurological examination, the sparse vocabulary used was very inarticulate and there was decreased attention. Motor examination revealed hypotonia and chorea, and deep tendon reflexes were hypoactive.

Twin B similarly presented with cognitive impairment and hyperactive behavior. Developmental assessment showed moderate intellectual disability with a WISC-III Full Scale IQ measurement of 38 and impairment of motor coordination along with hyperactive behavior. This patient had infantile onset of convulsive seizures at 3 months of age, treated with phenobarbital and without a recurrence since the age of 4 years. Phenobarbital was tapered off after two seizure-free years. Levetiracetam was initiated recently when the breakthrough seizure occurred in the twin brother.

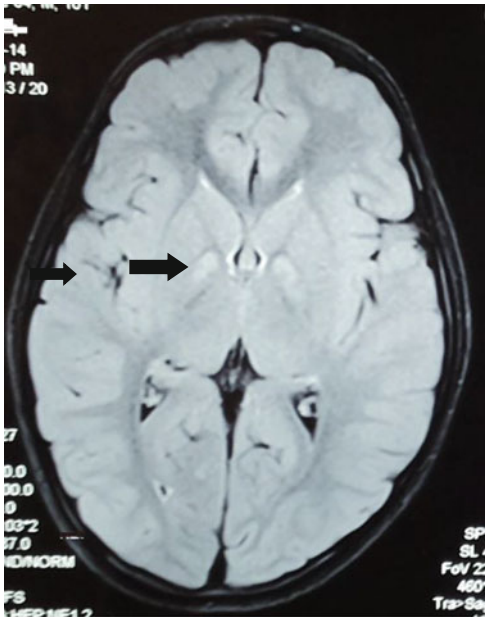

Fig. 1 Magnetic resonance imaging of the brain. Axial MRI FLAIR sequence with hyperintensities of globus pallidi (*arrowhead*)

There had been no gestational or perinatal complications. The developmental history similarly showed that hypotonia was noted in infancy at the time of seizure onset and there was delayed acquisition of milestones. Neurological examination showed minimal expressive and disarticulate language, hypotonia, and hyporeflexia.

Brain MRI was obtained in Twin A and showed symmetrical hyperintensities of the globus pallidi on T2-weighted and FLAIR sequences (Fig. 1). Urine was sent on both twins for organic acid analysis, and gas chromatography-mass spectrometry (GC-MS) revealed significantly increased levels of 4-hydroxybutyric acid and 4,5-dihydroxyhexanoic acid. These findings led to ALDH5A1 sequencing which revealed homozygous c.608C>T; pPro203Leu mutations, previously described as disease causing, in both subjects. The parents were confirmed as heterozygous as were two siblings.

Case ascertainment dating back to the initial report of gamma-hydroxybutyric aciduria identified 91 unique patients with clinical details provided (Aoshima et al. 2002; Bekri et al. 2004; Brown et al. 1987; Dayan et al. 2006; Deng et al. 2011; Divry et al. 1983; Escalera et al. 2010; Gogou et al. 2016; Haan et al. 1985; Ishiguro et al.

Table 1 Ethnicity/geographic distribution of reported SSADH deficiency cases

Country	Total
United States	43
Turkey	18
China	13
Saudi	10
Germany	9
Australia	7
Netherlands	7
UK	7
Pakistan	6
Greece	5
Spain	5
Iran	4
Japan	4
India	3
Ireland	3
Israel	3
Italy	3
Afghanistan	2
Argentina	2
Bulgaria	2
Canada	2
France	2
Korea	2
Lebanon	2
Lifu	2
Taiwan	2
Albania	1
Algeria	1
Belgium	1
Denmark	1
Inuit	1
Luxemburg	1
Malaysia	1
Sicily	1
Sweden	1
Syria	1
Tunisia	1
UAE	1
Uruguay	1
Yemen	1
Total	182

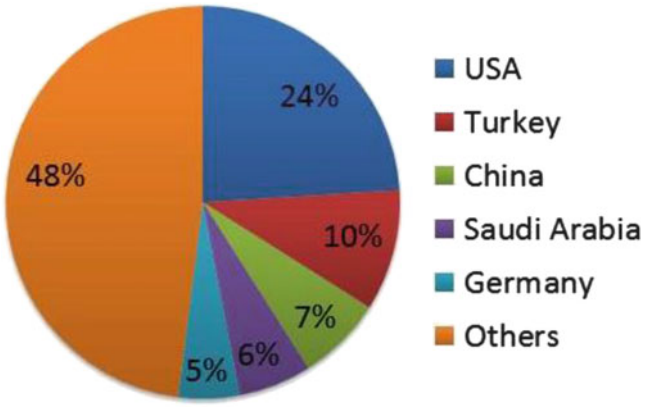

Fig. 2 Countries reporting cases of SSADH deficiency ($N = 40$)

2001; Jakobs et al. 1981; Jiang et al. 2013; Kratz 2009; Kwok et al. 2012; Lemes et al. 2006; Li et al. 2015; Lin et al. 2015; Liu et al. 2016; Neu et al. 2002; Niemi et al. 2014; O'Rourke et al. 2010; Onkenhout et al. 1989; Pearl et al. 2003; Peters et al. 1999; Puttmann et al. 2013; Racaru et al. 2010; Rashed et al. 1994; Rating et al. 1984; Saronwala et al. 2008; Spilioti et al. 2013; Tay et al. 2015; Wang et al. 2016; Yamakawa et al. 2012; Zhao et al. 2003; Ziyeh et al. 2002). We furthermore identified 91 additional subjects with confirmed SSADH deficiency in our database published in aggregate (Parviz et al. 2014). Overall, we were able to identify 182 unique cases of SSADH deficiency. The ethnicity of the patients is shown in Table 1; when only geographic residence was provided, this was used instead. There were a total of 40 ethnicities or countries represented in the patient population (Fig. 2). The countries with the greatest number of patients reported were the USA (24%), Turkey (10%), China (7%), Saudi Arabia (6%), and Germany (5%). Together, these five countries accounted for approximately half of all reported patients.

Discussion

The median age at diagnosis of SSADH deficiency is 2 years, but underdiagnosis is suspected. 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). An adult was recently diagnosed at age 62 during a terminal illness marked by repeated status epilepticus, although his family described a typical childhood course yet without a specific diagnosis or suspicion of a metabolic disorder (Lapalme-Remis et al. 2015). The phenotype typically is neurodevelopmental impairment with intellectual deficiency, marked expressive language impairment, and epilepsy. Typical neurological features include hypotonia, ataxia, and hyporeflexia with some patients manifesting chorea. The neuropsychiatric profile includes often disabling obsessive compulsive disorder and anxiety in addition to inattention, hyperactive behavior, and sleep disturbances (Gibson et al. 2003; Pearl et al. 2003).

This is the first report of a family from India since the relatively large series of patients that added 23 new cases to the literature in 1997 (Gibson et al. 1997). The previously reported family had three affected children, the oldest diagnosed posthumously based on a consistent phenotype with death at 13 years. The siblings in that family were diagnosed at ages 9 and 3 years, with laboratory detection using urine organic acids and confirmation based on enzyme activity determination.

The twins in the present report had a delay in diagnosis to 10 years of age and otherwise presented with delay of acquired infantile milestones, early hypotonia, intellectual deficiency, and marked impairment of expressive language. The infantile onset of epilepsy with remission in early childhood is less typical but does occur. Epilepsy often appears during later childhood or adolescence and is more prevalent in the adult than pediatric cohort (Lapalme-Remis et al. 2015). The findings on examination of hypotonia, chorea, and hyporeflexia are typical of the disorder. Globus pallidus hyperintensities on T2-weighted MRI and gamma-hydroxybutyric aciduria along with elevated 4,5-dihydroxy-hexanoic acid are diagnostic markers of the disorder (Pearl et al. 2009). Epileptiform discharges on EEG tend to be generalized but focal spikes have been described (Pearl et al. 2009). More than 35 ALDH5A1 mutations including missense, nonsense, and splice mutations have been reported. The c.608C>T; p.Pro203Leu mutation has been previously reported and affects an amino acid highly conserved across all known mammalian species and was undetected in approximately 1,300 control alleles (Akaboshi et al. 2003).

We were able to identify 182 subjects with SSADH deficiency based on the literature and our database, from 40 countries with five countries reporting half of all patients. The nonspecific phenotype of the disorder, usually following the pattern of a nonprogressive encephalopathy that may have superimposed epilepsy, mandates a high index of clinical suspicion for a metabolic disorder, and we suspect these are the countries with centers more likely to pursue metabolic diagnostic studies in this clinical scenario. Underdiagnosis, late diagnosis, and disproportional geographic representation are common as with other neurometabolic disorders.

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