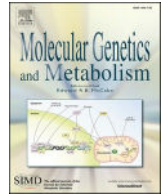


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## Consensus guidelines for the diagnosis and management of succinic semialdehyde dehydrogenase deficiency

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**Abbreviations:** AAV, adeno-associated virus; ADHD, attention-deficit/hyperactivity disorder; AGREE II, Appraisal of Guidelines for Research and Evaluation; ALDH5A1, aldehyde dehydrogenase 5 family member A1; ASD, autism spectrum disorder; ASM, anti-seizure medication; CSF, cerebrospinal fluid; EEG, electroencephalogram; GABA,  $\gamma$ -aminobutyric acid; GBA, guanidinobutyrate; GHB,  $\gamma$ -hydroxybutyrate; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; iNTD, International Working Group on Neurotransmitter related Disorders; LP, lumbar puncture; MRI, magnetic resonance imaging; NAA, N-acetylaspartate; NHS, natural history study; OCD, obsessive-compulsive disorder; PGD, preimplantation genetic diagnosis; SMA, supplementary motor area; SSADHD, succinic semialdehyde dehydrogenase deficiency; SSRI, selective serotonin reuptake inhibitor; VUS, variant of unknown significance.

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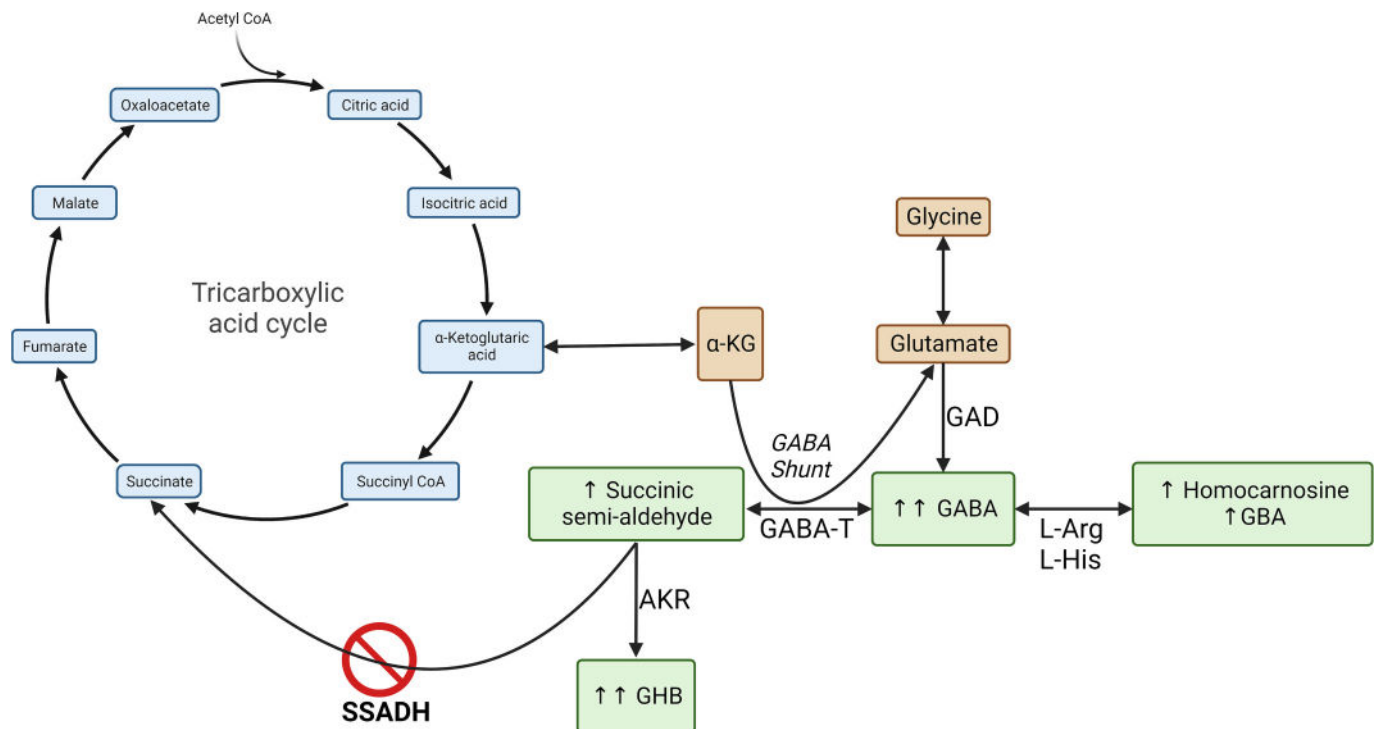
## ABSTRACT

Succinic semialdehyde dehydrogenase deficiency (SSADHD) (OMIM #271980) is a rare autosomal recessive metabolic disorder caused by pathogenic variants of *ALDH5A1*. Deficiency of SSADH results in accumulation of  $\gamma$ -aminobutyric acid (GABA) and other GABA-related metabolites. The clinical phenotype of SSADHD includes a broad spectrum of non-pathognomonic symptoms such as cognitive disabilities, communication and language deficits, movement disorders, epilepsy, sleep disturbances, attention problems, anxiety, and obsessive-compulsive traits. Current treatment options for SSADHD remain supportive, but there are ongoing attempts to develop targeted genetic therapies. This study aimed to create consensus guidelines for the diagnosis and management of SSADHD. Thirty relevant statements were initially addressed by a systematic literature review, resulting in different evidence levels of strength according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria. The highest level of evidence (level A), based on randomized controlled trials, was unavailable for any of the statements. Based on cohort studies, Level B evidence was available for 12 (40%) of the statements. Thereupon, through a process following the Delphi Method and directed by the Appraisal of Guidelines for Research and Evaluation (AGREE II) criteria, expert opinion was sought, and members of an SSADHD Consensus Group evaluated all the statements. The group consisted of neurologists, epileptologists, neuropsychologists, neurophysiologists, metabolic disease specialists, clinical and biochemical geneticists, and laboratory scientists affiliated with 19 institutions from 11 countries who have clinical experience with SSADHD patients and have studied the disorder. Representatives from parent groups were also included in the Consensus Group. An analysis of the survey's results yielded 25 (83%) strong and 5 (17%) weak agreement strengths. These first-of-their-kind consensus guidelines intend to consolidate and unify the optimal care that can be provided to individuals with SSADHD.

## 1. Introduction

Succinic semialdehyde dehydrogenase deficiency (SSADHD) (OMIM #271980) is an autosomal recessively inherited metabolic disorder resulting from bi-allelic pathogenic variants of *ALDH5A1*, a 38-kb gene mapped on chromosome 6p22 with an open reading frame of 1605 base pairs encoding 535 amino acids [National Center for Biotechnology Information (NCBI) reference sequence: NM\_001080.3] [1]. Deficiency or absence of the mitochondrial enzyme SSADH leads to impaired catabolism of  $\gamma$ -aminobutyric acid (GABA), the brain's predominant inhibitory neurotransmitter. The biochemical consequences of this

faulty metabolic pathway include the accumulation of GABA and GABA-related metabolites, such as  $\gamma$ -hydroxybutyrate (GHB) and guanidinobutyrate (GBA) (Fig. 1). Supraphysiological concentrations of these neurotransmitters are believed to cause use-dependent downregulation of GABA receptors and show a maturational decline with age [2,3]. Disruption of GABA homeostasis and imbalance between brain excitatory and inhibitory neurotransmission are thought to be the root of the major developmental and neurologic manifestations of individuals with SSADHD. However, heterozygosity and the resulting combination of pathogenic *ALDH5A1* variants produce SSADH enzymes with significant differences in structure and function, differences which are believed to



**Fig. 1.** The metabolic pathway impairment in succinic semialdehyde dehydrogenase deficiency (SSADHD).  $\alpha$ -KG-  $\alpha$ -ketoglutaric acid (2-oxoglutaric acid); AKR- aldo-keto reductase; GABA-  $\gamma$ -aminobutyrate; GABA-T- GABA transaminase; GAD- glutamic acid decarboxylase; GBA- guanidinobutyrate; GHB-  $\gamma$ -hydroxybutyrate; L-Arg- L-arginine; L-His- L-histidine; SSADH- succinic semialdehyde dehydrogenase;

explain the broad and variable clinical presentation of SSADHD [4,5]. The main clinical features of SSADHD include cognitive and adaptive disabilities, communication and language deficits, epilepsy, autism spectrum disorder (ASD), movement disorders (such as ataxia, dystonia, and exertional dyskinesia), sleep disturbances, attention problems, anxiety, and obsessive-compulsive traits [6]. Current treatments are solely supportive and symptomatic. However, ongoing investigations aim to establish gene and enzyme replacement therapies for SSADHD [7].

The estimated prevalence of SSADHD in developed countries is ~1/460,000 [8]. The rarity and non-pathognomonic clinical phenotype of SSADHD, presenting in different degrees of severity and at different ages, often leads to misdiagnosis or late diagnosis of the condition. Moreover, healthcare professionals unaccustomed to the management of individuals with SSADHD may be misguided by reliance on outdated literature. In 2019, a 5-year SSADHD Natural History Study (NHS) was initiated by investigators of the SSADHD Deficiency Research Consortium with funding from the Eunice Kennedy Shriver National Institute of Child Health and Development (NIH R01 1R01HD091142) [9]. This prospective study included Boston Children's Hospital (Boston, MA, USA) as the primary clinical site and three European sites (University Children Hospital Heidelberg, Germany, Sant Joan de Déu Barcelona Children's Hospital, Spain, and Oslo University Hospital, Oslo, Norway), as well as the International Working Group on Neurotransmitter related Disorders (iNTD). Data management was provided by the University of South Florida, and bioanalytical variant analyses were completed at the University of Verona, Italy.

The clinical and bioanalytical investigations of individuals enrolled in the SSADHD NHS-derived clinical experience and comprehensive data, along with input from international rare disease experts and collaborators provided the most comprehensive and up-to-date information on definition, epidemiology, clinical presentation, recommended diagnostic investigation, and management of the disorder. This information was used, in turn, to create the guidelines presented in this report. The process included a systematic review and analysis of the literature using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method, and subsequent expert opinion sought from worldwide clinicians caring for individuals with SSADHD and investigators studying the disorder. The study's workflow was directed by the Appraisal of Guidelines for Research and Evaluation (AGREE II) criteria [10]. This report represents the first-of-its-kind clinical guidelines of SSADHD, intending to solidify and bring together the best possible care that can be provided to individuals with this disorder.

## 2. Materials and methods

### 2.1. Guidelines establishment

The guidelines were formed by an "SSADHD Consensus Group" established for the objectives of this study. This inclusive group comprised members of the SSADHD Deficiency Research Consortium, additional experts caring for individuals with SSADHD worldwide, and representatives of the SSADHD Association, a US-based patient advocacy group representing over 150 families worldwide. Overall, the SSADHD Consensus Group included 23 participants from 19 institutions of 11 countries from four continents. The distribution of healthcare professionals of the group consisted of neurologists, metabolic specialists, neuropsychologists, clinical and biochemical geneticists, laboratory scientists, and representatives from parent groups. SSADHD Consensus Group committee members (ITL, JBR, and PLP) drafted statements that reflect the definition, epidemiology, clinical presentation, diagnosis, and management of SSADHD. These statements were sent to all the group's participants. Following their review and editing, the statements were presented in a virtual meeting, including all the group's members, in which they were discussed, revised, and finalized. Once the statements were established, the strength of the evidence supporting them was

determined through a systematic literature review and an expert-opinion consensus, as described in detail below.

### 2.2. Systematic literature review

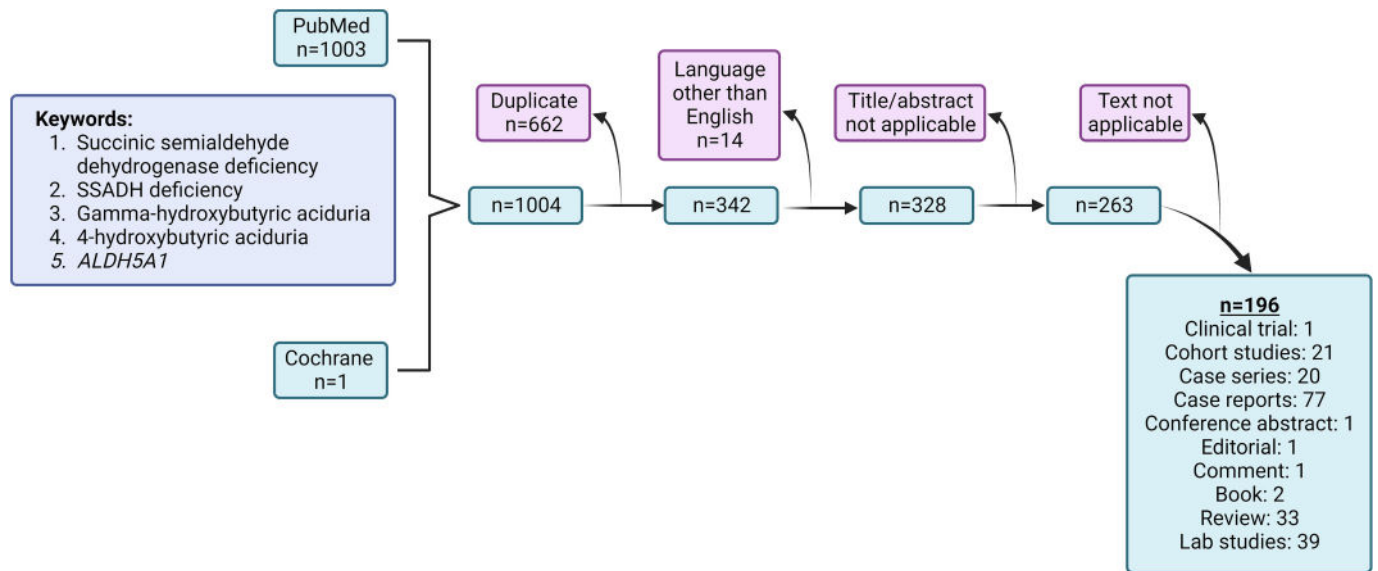
We carried out a systematic literature review of SSADHD-related publications from the PubMed and Cochrane databases. The search included all the English-written peer-reviewed manuscripts published since 1981 (the year the first case report of SSADHD was published [11]) until October 2023 containing the keywords succinic semialdehyde dehydrogenase deficiency, SSADHD deficiency, gamma-hydroxybutyric aciduria, 4-hydroxybutyric aciduria, and *ALDH5A1*. The preliminary search identified 1004 entries, from which a total of 808 were discarded: 662 for being duplicates, 14 for being in languages other than English, and 65 and 67 for consisting of a non-applicable title/abstract and text, respectively. The remaining valid 196 publications consisted of  $n = 1$  clinical trial,  $n = 21$  cohort studies,  $n = 20$  case series,  $n = 77$  case reports,  $n = 1$  conference abstract,  $n = 1$  editorial,  $n = 1$  comment,  $n = 2$  books,  $n = 33$  reviews, and  $n = 39$  laboratory studies (Fig. 2).

### 2.3. Strength of evidence

The strength of the systematic literature review-derived evidence found for each of the study's statements was assessed using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) [12]. According to this method, evidence strength is determined by the study type, biases, and effect size and graded as high, moderate, low, or very low (Table 1). Apart from a single study that failed to demonstrate clinical efficacy for SGS-742, a GABA<sub>B</sub> receptor antagonist [13], until this time, there have not been any prospective randomized controlled trials evaluating relevant diagnostic or therapeutic matters of SSADHD. As a result, none (0%) of the statements curated for this study were answered by high-quality (level A) evidence. However, 12 (40%) of the study's statements were met with moderate-quality (level B) evidence derived from the SSADHD cohort studies published so far. Evidence for the remaining 18 (60%) statements was graded as low (level C) or very low (level D).

### 2.4. Expert-opinion consensus

Due to the insufficient high-quality (level A) evidence for SSADHD, as is the case with most inherited metabolic disorders [14], an expert opinion was sought for all the statements using the Delphi methodology [15]. Web-mediated surveys including the statements agreed upon by the SSADHD Consensus Group were prepared and distributed via Qualtrics (Qualtrics, Provo, UT, USA) with a personal link to each member of the Consensus Group. The survey remained accessible and active for six weeks after distribution. Each statement included five response options (*completely agree*, *mostly agree*, *partially agree*, *mostly disagree*, *completely disagree*) and a *non-applicable* option for those who felt their field of expertise did not qualify them to give an expert opinion on the statement. A total of 22 (95%) members of the SSADHD Consensus Group completed all (100%) of the survey's items. Agreement consensus on statements was reached when  $\geq 66\%$  of the qualified opinions were either *completely agree* or *mostly agree*. Conversely, disagreement consensus was reached when  $< 66\%$  of the qualified opinions mostly disagreed or completely disagreed. Overall, consensus was achieved for 30 (100%) of the 30 statements. The strength of the statements was estimated using the responses of those in the Consensus Group who felt qualified to give an expert opinion. Strength was defined as "strong" when  $\geq 90\%$  of the experts completely or mostly agreed with the statements and "weak" when  $< 90\%$  mostly or completely disagreed (Table 1). Twenty-five (83%) of the 30 statements were completely or mostly agreed upon by Consensus Group members, resulting in a majority of strong agreements. Survey outcomes were then presented to the SSADHD Consensus Group in an inclusive second virtual meeting. For



**Fig. 2.** A flowchart specifying the literature review process of succinic semialdehyde dehydrogenase deficiency (SSADHD)-related evidence.

**Table 1**  
Strength of evidence and SSADHD Consensus Group expert-agreement.

Evidence strength	Definition
A- High-quality evidence	Randomized control studies, high confidence in effect estimates
B- Moderate-quality evidence	Cohort studies, moderately confident in effect estimate
C- Low-quality evidence	Observational studies, confidence in effect estimate is limited
D- Very-low quality evidence	Expert opinions, limited confidence in the effect estimate
Agreement strength	Definition
Strong agreement	The statement is applicable to all SSADHD individuals, and supported by a high expert-opinion agreement ( $\geq 90\%$ )
Weak agreement	The statement is applicable to some SSADHD individuals, is circumstance-dependent, and is not supported by a high expert-opinion agreement ( $< 90\%$ )

guidance of this process, we also used the AGREE II criteria [10].

### 3. Results

#### 3.1. Definition

**Statement 1.** SSADHD is an autosomal recessive inherited metabolic disorder caused by pathogenic bi-allelic variants in *ALDH5A1*, leading to decreased or absent activity of the enzyme SSADH, resulting in impairment of GABA catabolism.

- Level of evidence: B
- Expert opinion: completely agree (90%), mostly agree (5%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (5%); [N = 20/20 (100%) completely or mostly agreed].
- Strength of agreement: Strong

In 1981, the deficiency of SSADH was first postulated to explain the excretion of GHB and succinic semialdehyde in an individual presenting intellectual disability and other neurologic abnormalities [11]. During the 1980s and 1990s, SSADHD was established as an inherited metabolic disorder, as many other case reports and laboratory studies provided evidence of this metabolic impairment in the degradation pathway of GABA [16–26]. The genetic origin of SSADHD was first reported in 1998

[27]. Since then, several case series and cohort studies have invariably described that the clinical phenotype and biochemical phenotype of SSADHD derive from pathogenic bi-allelic variants in *ALDH5A1* [1,28–32].

#### 3.2. Epidemiology

**Statement 2.** SSADHD is a rare inherited metabolic disorder spanning across all ethnicities, with a reported estimated prevalence of  $\sim 1/500,000$ .

- Level of evidence: B
- Expert opinion: completely agree (57%), mostly agree (29%), partially agree (5%), mostly disagree (5%), completely disagree (0%), non-applicable (5%); [N = 18/20 (90%) completely or mostly agreed].
- Strength of agreement: Strong

There have been  $\sim 450$  SSADHD individuals whose details have been published thus far in the medical and scientific literature [33,34]. Considering the non-pathognomonic clinical signs and symptoms of SSADHD and the fact that metabolic screening worldwide is limited to a few highly specialized laboratories, it is difficult to estimate the exact prevalence of SSADHD [6,34]. However, a recent study that relied on population, exome, and whole genome databases estimated the pan-ethnic carrier frequency of SSADHD at  $\sim 1/340$  and worldwide prevalence at  $\sim 1/460,000$  [8].

#### 3.3. Clinical manifestations and onset

**Statement 3.** The clinical presentation of SSADHD is nonspecific and may include any of these manifestations: intellectual disability, language difficulties, hypotonia, motor function deficits, movement disorders, seizures, disruptive behaviors, autistic behaviors such as problems with social communication and stereotypies, anxiety, attention problems, obsessive-compulsive traits, and sleep disturbances.

- Level of evidence: B
- Expert opinion: completely agree (90%), mostly agree (5%), partially agree (0%), mostly disagree (5%), completely disagree (0%), non-applicable (0%); [N = 20/21 (95%) completely or mostly agreed].

- Strength of agreement: Strong

Based on many case reports [35–50] and several case series [51–55] and cohort studies [6,9,30,56–61], the clinical signs and symptoms listed in this statement were found to be reported most consistently in individuals with SSADHD.

**Statement 4.** . Hallucinations, delusions, and ideas of reference may be part of the clinical presentation of SSADHD.

- Level of evidence: C
- Expert opinion: completely agree (43%), mostly agree (24%), partially agree (10%), mostly disagree (5%), completely disagree (0%), non-applicable (19%); [ $N = 14/17$  (82%) completely or mostly agreed].
- Strength of agreement: Weak

There have been several case reports describing features associated with psychosis in individuals with SSADHD [43,62]. Based on the lower level of evidence of these psychiatric manifestations and the weak expert opinion agreement, we cannot definitely affirm they constitute one of the main manifestations of this disorder, and future studies should explore their occurrence rate and characteristics in SSADHD.

**Statement 5.** . Cerebrovascular accidents, neuroleptic malignant syndrome, hypothyroidism, and strabismus have been reported in individuals with SSADHD but do not have a known association with the disorder.

- Level of evidence: C
- Expert opinion: completely agree (33%), mostly agree (33%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (29%).
- Strength of agreement: Strong.

The clinical signs and symptoms listed in this statement have been inconsistently reported in SSADHD by case reports (cerebrovascular accident [63,64], neuroleptic malignant syndrome [65], hypothyroidism [66], and strabismus [67]) and are not considered part of the classic or expected presentation of this disorder. Until further evidence and observations specify otherwise, we cannot determine that these conditions are directly associated with the SSADHD phenotype and may have coincidentally occurred in those individuals in whom they were reported.

**Statement 6.** . The clinical signs and symptoms of SSADHD may present at any age and with different degrees of severity, with most individuals having symptoms in the first year.

- Level of evidence: B
- Expert opinion: completely agree (62%), mostly agree (24%), partially agree (0%), mostly disagree (5%), completely disagree (0%), non-applicable (29%); [ $N = 18/19$  (95%) completely or mostly agreed].
- Strength of agreement: Strong

Evidence from case reports and case series indicate SSADHD may present mildly [68,69] or severely [37,70–72], even among siblings [45,73]. Variability in the severity of the clinical phenotype and its onset (symptomatology typically present in the first year of life but may present at any age) has also been demonstrated in extensive cohort studies [5,6,56,61,74–76].

**Statement 7.** . As individuals with SSADHD age, epilepsy severity, behavioral difficulties, and psychiatric traits may worsen, but communication and adaptive skills may improve.

- Level of evidence: B

- Expert opinion: completely agree (38%), mostly agree (43%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (14%); [ $N = 17/18$  (94%) completely or mostly agreed].
- Strength of agreement: Strong

Existing moderate-level evidence suggests that the general clinical severity [5,39,76–79], and specifically that of seizures [56], autism symptoms [74], and psychiatric manifestations [60,80] of subjects with SSADHD increases with age, usually in a slowly progressive manner [58]. In contrast, the data suggest that communication and adaptive skills improve with age [5].

**Statement 8.** . Individuals with SSADHD may develop exertional dyskinesia, typically in late adolescence or early adulthood, with dystonic posturing or hemiballismus.

- Level of evidence: B
- Expert opinion: completely agree (43%), mostly agree (19%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (33%); [ $N = 13/14$  (93%) completely or mostly agreed].
- Strength of agreement: Strong

Possibly originating from cerebral excitation:inhibition imbalance, and driven by a GABA<sub>B</sub>-ergic motor cortex dysfunction [81], movement disorders such as exertional dyskinesia, dystonic posturing, and hemiballismus may develop in infancy [71], but mostly in late adolescence or early adulthood of individuals with SSADHD [58,76,78,82].

### 3.4. Diagnosis

**Statement 9.** . A diagnosis of SSADHD should be considered for an individual at any age presenting with clinical manifestations associated with the disorder.

- Level of evidence: C
- Expert opinion: completely agree (67%), mostly agree (19%), partially agree (10%), mostly disagree (0%), completely disagree (0%), non-applicable (5%); [ $N = 18/20$  (90%) completely or mostly agreed].
- Strength of agreement: Strong

This statement aims to raise awareness about the broad and non-specific clinical spectrum of SSADHD and potential onset later in life [9,58,78]. Thus, a diagnostic investigation of SSADHD should be considered for individuals at any age when facing unexplained symptoms that are part of the clinical phenotype.

**Statement 10.** . The standard biochemical laboratory screening test for SSADHD is urine organic acids to detect increased  $\gamma$ -hydroxybutyric acid (GHB). False positive results may stem from urine collection via a catheter or in patients receiving exogenous sources of GHB, e.g., for sedation or illicit substance abuse.

- Level of evidence: B
- Expert opinion: completely agree (71%), mostly agree (19%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (5%); [ $N = 19/20$  (95%) completely or mostly agreed].
- Strength of agreement: Strong

Detection of  $\gamma$ -hydroxybutyric acid in urine is the primary and most accessible biochemical laboratory method to diagnose SSADHD [9]. Since urine collected from a catheter [83] or following the patient's sedation with GHB [84] may lead to false positive  $\gamma$ -hydroxybutyric

aciduria, awareness of these clinical situations is advised in the setting of SSADHD diagnosis. Notably, false-negative results missing the GHB peak may also occur [6]. Hence, genetic testing with phenotype-directed gene sequencing panels or whole exome or genome sequencing are complementary and confirmatory diagnostic methods. While increased systemic or cerebral GABA and other GABA-related metabolites may also suggest the diagnosis of SSADHD [76,85], these methods are performed in specialized laboratories and are not recommended for initial screening.

**Statement 11.** . If the clinical presentation suggests SSADHD, gene sequencing demonstrating two pathogenic variants of *ALDH5A1* provides laboratory confirmation of the diagnosis. In case one or two *ALDH5A1* variants of unknown significance (VUSs) result, the diagnosis can be made by correlation with the clinical phenotype and persistent  $\gamma$ -hydroxybutyric aciduria.

- Level of evidence: B
- Expert opinion: completely agree (57%), mostly agree (29%), partially agree (0%), mostly disagree (10%), completely disagree (0%), non-applicable (5%); [N = 18/20 (90%) completely or mostly agreed].
- Strength of agreement: Strong

Definite confirmation of the diagnosis of SSADHD can be achieved by genetic testing demonstrating the presence of bi-allelic variants in *ADLH5A1* [1,28–30,37,53,69,70,86–90]. Further assessment of the variants' pathogenicity may be accomplished by in silico functional analyses [4]. In subjects for whom one or two *ALDH5A1* variants are revealed and determined as "variants of unknown significance (VUSs)," the diagnosis of SSADHD can be made by correlation with the clinical phenotype and persistent  $\gamma$ -hydroxybutyric aciduria.

**Statement 12.** . Genetic testing demonstrating that family members carry a pathogenic variant in *ALDH5A1* should be considered for family planning, prenatal diagnosis, and preimplantation genetic diagnosis (PGD).

- Level of evidence: D
- Expert opinion: completely agree (76%), mostly agree (14%), partially agree (5%), mostly disagree (5%), completely disagree (0%), non-applicable (0%); [N = 19/21 (90%) completely or mostly agreed].
- Strength of agreement: Strong

Since SSADHD is an autosomal recessive disorder, genetic testing to assess the carrier status of parents, siblings, and other family members of SSADHD patients is recommended for family planning purposes. The pursuit of carrier screening should follow a mutual decision-making process between healthcare providers and families and be guided by the families' subjective preferences and cultural values [91].

**Statement 13.** . Lumbar puncture (LP) for cerebrospinal fluid (CSF) collection is not required to confirm the diagnosis of SSADHD.

- Level of evidence: D
- Expert opinion: completely agree (90%), mostly agree (5%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (5%); [N = 20/20 (100%) completely or mostly agreed].
- Strength of agreement: Strong

In contrast to some other inherited neurotransmitter disorders, the diagnosis of SSADHD can be completed by less invasive tests such as a urine test or a genetic test (attained from saliva or plasma). Therefore, while CSF showing elevated GABA levels may be supportive, it is not required for diagnosis [92]. CSF analyses may be relevant for prognostication and treatment planning in the future. To that end, an array of

CSF biomarkers is available [93].

**Statement 14.** . An electroencephalogram (EEG) is indicated for individuals with SSADHD presenting with seizures or suspected seizures.

- Level of evidence: B
- Expert opinion: completely agree (81%), mostly agree (10%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (10%); [N = 19/19 (100%) completely or mostly agreed].
- Strength of agreement: Strong

The most common EEG patterns seen in SSADHD are generalized (diffuse) background slowing and focal or multifocal epileptiform activity in the form of spikes or sharp waves, with or without slow waves [56,59]. EEGs may also be abnormal in individuals with SSADHD who do not have seizures [56]. Treatment with anti-seizure medications is not indicated for individuals without seizures who have EEG abnormalities. Hence, an EEG is not indicated in SSADHD unless there is clinical suspicion of seizures.

**Statement 15.** . Brain MRI may be used to rule out other conditions that cause the clinical phenotype but is not required to establish a diagnosis of SSADHD.

- Level of evidence: B
- Expert opinion: completely agree (81%), mostly agree (10%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (10%); [N = 19/19 (100%) completely or mostly agreed].
- Strength of agreement: Strong

The typical neuroimaging findings of SSADHD include magnetic resonance imaging (MRI) T2-weighted signal hyperintensities in the globus pallidi, subthalamic nuclei, and cerebellar dentate nuclei. More rarely, other abnormalities, such as cortical and cerebellar atrophy, may be seen [94]. Magnetic resonance spectroscopy may show an increased GABA/N-acetylaspartate (NAA) ratio [94]. While these findings consistently appear in SSADHD, they are not diagnostic of the disorder, nor do they have specific therapeutic implications. Neuroimaging is not specifically indicated for SSADHD, unless neurological signs warranting a neuroimaging assessment are present [95].

### 3.5. Management

**Statement 16.** . The care of an individual with SSADHD should include a multidisciplinary team, including experts in genetic-metabolic disease and neurology.

- Level of evidence: D
- Expert opinion: completely agree (81%), mostly agree (10%), partially agree (0%), mostly disagree (10%), completely disagree (0%), non-applicable (0%); [N = 19/21 (90%) completely or mostly agreed].
- Strength of agreement: Strong

The multiple manifestations affecting SSADHD patients involve various healthcare disciplines. Due to the rarity of the disorder and its predominant neurological impairments, it is advisable that neurologists and experts in metabolic disease or clinical geneticists be the principal healthcare providers of SSADHD individuals.

**Statement 17.** . A neuropsychological or psychoeducational assessment is indicated for individuals with SSADHD at the time of diagnosis and monitored periodically to assess whether appropriate therapeutic interventions are needed.

- Level of evidence: C
- Expert opinion: completely agree (76%), mostly agree (10%), partially agree (5%), mostly disagree (0%), completely disagree (5%), non-applicable (5%); [N = 19/21 (90%) completely or mostly agreed].
- Strength of agreement: Strong

Existing evidence indicates that the vast majority of subjects with SSADHD have intellectual disabilities and adaptive function deficits that may worsen with age. Moreover, ASD has an occurrence rate of ~50% in SSADHD, and ASD symptoms may appear later in the lives of SSADHD subjects compared to non-syndromic ASD [35,40,74,96]. After the age of ~7 years, there is a higher likelihood of emergence of ASD symptoms as well as potential increase in severity of previously exhibited ASD-associated behaviors. [74]. Considering the above and the potential for early interventions to improve (or mitigate the regression of) cognitive and adaptive functions as well as ASD symptoms [97–101], it is recommended that individuals with SSADHD undergo a neuropsychological or psychoeducational assessment at diagnosis and regularly thereafter to track their progress, provide individually tailored interventions, and refine diagnostic profiles.

**Statement 18.** . Individuals with SSADHD should be evaluated for physical and occupational therapy commensurate to the severity of their motor function deficits.

- Level of evidence: D
- Expert opinion: completely agree (76%), mostly agree (0%), partially agree (5%), mostly disagree (5%), completely disagree (0%), non-applicable (14%); [N = 16/18 (88%) completely or mostly agreed].
- Strength of agreement: Weak

The majority of SSADHD individuals have gross and fine motor deficits [6,61,102]. Notwithstanding their severity, motor deficits impact day-to-day activities and are a major concern for caretakers [103]. Members of the Consensus Group agreed that physical and occupational therapies should be provided to anyone with SSADHD who requires them, but there was a weak strength of agreement that these functions should be assessed in the absence of clinical concerns.

**Statement 19.** . Individuals with SSADHD are expected to require special educational services and individualized education plans in school.

- Level of evidence: D
- Expert opinion: completely agree (81%), mostly agree (14%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (0%); [N = 20/21 (95%) completely or mostly agreed].
- Strength of agreement: Strong

The vast majority of individuals with SSASH have cognitive, motor, behavioral, social, academic, and psychological difficulties. Depending on access, availability, and the policies of local education systems, they should be provided with special educational services. Providers should work closely with families and local school systems to ensure appropriate, individualized, assessment-based recommendations for special services are incorporated into the education program. This may include physical, occupational, speech, and behavioral therapies, academic support, psychological support, and social skills therapy. This may increase their level of functioning and alleviate their caregivers' and own burden [104].

**Statement 20.** . Individuals with SSADHD are anticipated to require speech and augmentative communication therapy.

- Level of evidence: C

- Expert opinion: completely agree (76%), mostly agree (14%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (5%); [N = 19/20 (95%) completely or mostly agreed].
- Strength of agreement: Strong

Clinical observations show that individuals with SSADHD often have better receptive than expressive language functions, and dysfunction in the supplementary motor area (SMA) subserving speech (pre-SMA) and its connections with other cortical and subcortical areas associated with expressive language and auditory perception have been implicated [105]. Individuals with SSADHD should have a comprehensive speech therapy assessment and cognitively appropriate therapeutic intervention given either through private or special education services. Depending on their cognitive and motor skills, they may be candidates for a “total communication system” and individual communication techniques such as gestural training, picture exchange communication (real items, photos, or cartoons, depending on the level of cognitive functioning), sign language (depending on cognitive and motor functioning), and a computer-based augmentative communication device [106,107]. Periodic re-evaluation of speech and language skills is important to adjust therapy goals and strategies as needed over the lifespan.

**Statement 21.** . Behavioral therapy for individuals with SSADHD diagnosed with an autism spectrum disorder (ASD) should be initiated as early as possible.

- Level of evidence: D
- Expert opinion: completely agree (81%), mostly agree (5%), partially agree (0%), mostly disagree (0%), completely disagree (5%), non-applicable (10%); [N = 18/19 (95%) completely or mostly agreed].
- Strength of agreement: Strong

Established evidence supports early behavioral interventions for syndromic and non-syndromic ASD [97,108]. Our Consensus Group also strongly agreed that if feasible, behavioral therapies should be offered to SSADHD individuals with ASD.

**Statement 22.** . Seizures in SSADHD are predominantly generalized but may be focal in onset and are treated with antiseizure medications based on standard practice using seizure semiology and EEG.

- Level of evidence: B
- Expert opinion: completely agree (62%), mostly agree (14%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (24%); [N = 16/16 (100%) completely or mostly agreed].
- Strength of agreement: Strong

There is still uncertainty about the most suitable anti-seizure medication (ASM) in SSADHD. Depending on the types of seizures and epilepsy, case reports and series [33,109,110] have reported the use of levetiracetam or lamotrigine, either as monotherapy or in combination with carbamazepine, oxcarbazepine, and clobazam. The largest cohort study of SSADHD subjects that addressed their epilepsy characteristics provided some affirmation of the efficacy of the ASMs listed above [56]; however, this study was noninterventional, and clear-cut conclusions about ASMs cannot be drawn from it. Based on clinical experience, topiramate and zonisamide have also been used successfully in this patient population.

Apart from the specific ASMs vigabatrin, tiagabine, and valproate, which warrant special consideration (addressed in statements 23 and 24), ASMs should be given to individuals with SSADHD based on standard practice in epilepsy [111–113].

**Statement 23.** . The anti-seizure medications vigabatrin and tiagabine

result in further elevation of GABA levels, have shown little efficacy in SSADHD, and are not generally recommended.

- Level of evidence: B
- Expert opinion: completely agree (76%), mostly agree (5%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (19%); [N = 17/17 (100%) completely or mostly agreed].
- Strength of agreement: Strong

In theory, vigabatrin could be a rational therapy in SSADHD due to its properties, including inhibition of GABA-transaminase and resultant decrease in GHB levels, although the decrease is not sustained [114]. In practice, it may result in further exacerbation of elevated GABA levels, and its clinical effects have been inconsistent and without convincing efficacy [115–125]. For these reasons and its potential for retinotoxicity [126], vigabatrin is not generally recommended as an ASM for SSADHD.

**Statement 24.** . For an individual with SSADHD, valproate may inhibit residual enzymatic activity or impair mitochondrial function and is relatively contraindicated.

- Level of evidence: C
- Expert opinion: completely agree (62%), mostly agree (24%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (14%); [N = 18/18 (90%) completely or mostly agreed].
- Strength of agreement: Strong

Despite valproate's properties, which include inhibition of residual SSADHD activity [18,127,128], its efficacy for SSADHD has been occasionally described [129,130]. Valproate is not recommended as a first-line option ASM in SSADHD; however, it may be considered in circumstances such as medically refractory generalized spike-wave when other ASMs are ineffective.

**Statement 25.** . The ketogenic diet has not been demonstrated to be of clinical benefit in SSADHD.

- Level of evidence: D
- Expert opinion: completely agree (48%), mostly agree (24%), partially agree (14%), mostly disagree (0%), completely disagree (0%), non-applicable (14%); [N = 15/18 (83%) completely or mostly agreed].
- Strength of agreement: Weak

There are reports indicating that the ketogenic diet normalizes EEG abnormalities and ataxia, delays mortality, and rescues the SSADHD phenotype in murine models of the disorder [131–133]. However, evidence of efficacy in humans is lacking; thus, until further demonstration of its clinical benefit is obtained, the ketogenic diet is not clearly indicated as standard therapy in SSADHD [134]. However, if compliance is tolerated, it is not contraindicated and may be attempted.

**Statement 26.** . Treatment with taurine has not been shown to improve symptoms and clinical outcomes in SSADHD individuals.

- Level of evidence: B
- Expert opinion: completely agree (62%), mostly agree (10%), partially agree (0%), mostly disagree (0%), completely disagree (0%), non-applicable (29%); [N = 15/15 (100%) completely or mostly agreed].
- Strength of agreement: Strong

Despite promising therapeutic outcomes in a murine model of SSADHD [135,136], the efficacy of taurine treatment has not been demonstrated in clinical trials [137,138]. Correspondingly, there is no knowledge of any other alternative therapy that has shown efficacy in

SSADHD.

**Statement 27.** . Behavioral difficulties such as defiance or aggression that have not responded to behavioral interventions may be treated with benzodiazepines or atypical antipsychotics such as risperidone and aripiprazole.

- Level of evidence: C
- Expert opinion: completely agree (57%), mostly agree (10%), partially agree (10%), mostly disagree (5%), completely disagree (0%), non-applicable (19%); [N = 14/17 (82%) completely or mostly agreed].
- Strength of agreement: Weak

Behavioral therapy should typically be the first-line intervention for behavioral difficulties in SSADHD. Several case reports have described their experience treating behavioral problems in SSADHD [43,62,139] and suggested benzodiazepines or atypical antipsychotics may be effective. However, only a weak agreement supports this statement, primarily from a lack of established clinical experience.

**Statement 28.** . Anxiety, mood fluctuation, and obsessive-compulsive traits that have not responded to behavioral interventions may respond to selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine and escitalopram. Pramipexole has been reported as beneficial for obsessive-compulsive disorder (OCD) symptoms.

- Level of evidence: C
- Expert opinion: completely agree (57%), mostly agree (19%), partially agree (5%), mostly disagree (0%), completely disagree (0%), non-applicable (19%); [N = 16/17 (94%) completely or mostly agreed].
- Strength of agreement: Strong

These medications have not shown evidence-based efficacy in SSADHD [36,60,62,139]. However, the expert opinion is that SSRIs are efficacious and indicated for depression, anxiety, and OCD in individuals with SSADHD.

**Statement 29.** . Treatment of attention problems or a diagnosis of attention-deficit/hyperactivity disorder (ADHD) can be attempted with stimulants (such as methylphenidate or mixed amphetamine salts) or non-stimulant medications (such as atomoxetine).

- Level of evidence: D
- Expert opinion: completely agree (48%), mostly agree (14%), partially agree (5%), mostly disagree (5%), completely disagree (0%), non-applicable (29%); [N = 13/15 (87%) completely or mostly agreed].
- Strength of agreement: Weak

Behavioral therapy should typically be the first-line intervention for ADHD symptoms in SSADHD. Several reports suggest stimulants may successfully ameliorate these symptoms as well [60,62,139]. Nevertheless, there was only weak expert opinion agreement on this matter. Based on clinical observations, stimulants may be attempted for ADHD symptoms in SSADHD; however, they should be used with caution as they may lead to an increase in ADHD-related symptoms or unwanted side effects such as aggressiveness and irritability.

**Statement 30.** . Enzyme, mRNA, and gene replacement therapies are rational targeted approaches to SSADHD currently tested in preclinical studies.

- Level of evidence: C
- Expert opinion: completely agree (81%), mostly agree (14%), partially agree (0%), mostly disagree (0%), completely disagree



(0%), non-applicable (5%); [N = 20/20 (100%) completely or mostly agreed].

- Strength of agreement: Strong

Preclinical proof-of-concept studies in murine models have shown that enzyme replacement therapy [7,109] or liver-directed viral gene transfer [140] increases survival and improves SSADHD-related symptoms [31]. Preliminary results using an adeno-associated virus (AAV)-based brain-wide gene replacement therapy suggested a molecular reversal in murine models is associated with a phenotypic rescue upon treatment at the symptomatic stage. Based on these findings, there are ongoing efforts to develop clinically applicable targeted therapies for SSADHD [141,142].

#### 4. Conclusions

A comprehensive review of the literature and input from the largest group of international experts in SSADHD ever assembled led to these guidelines with consensus on the definition, epidemiology, clinical presentation, diagnosis, and management of SSADHD (Fig. 3).

With an estimated prevalence of approximately 1/500,000, SSADHD is an ultra-rare inherited metabolic disorder caused by bi-allelic pathogenic variants in *ALDH5A1*. The core signs and symptoms of the disorder include intellectual disability, prominent expressive language impairment, movement and motor function disorders, epilepsy, autism, anxiety, attention problems, obsessive-compulsive traits, and sleep

disturbances. Most individuals with SSADHD present in the first year of life; however, later onset can occur at any age and with different degrees of severity. It follows that a diagnosis of SSADHD should be considered independently of age for anyone presenting with one or more of the aforementioned manifestations. The standard laboratory biochemical diagnostic test for SSADHD is urine organic acids, revealing elevated  $\gamma$ -hydroxybutyric acid (4-hydroxybutyrate, or GHB). Confirmation of the diagnosis is achievable through gene sequencing demonstrating two pathogenic variants of *ALDH5A1*. Cases in which the clinical phenotype and persistent  $\gamma$ -hydroxybutyric aciduria coincide with *ALDH5A1* variants of unknown significance (VUSs) are also diagnostic of the disorder. Brain MRI and EEG are not diagnostic of SSADHD but are indicated if clinically relevant. Metabolic disease specialists or clinical geneticists and neurologists should manage individuals with SSADHD. Baseline and periodic neuropsychological assessments, including specific recommendations for school and individual therapies depending on the symptom presentation, are strongly advised. Accordingly, supportive physical, occupational, and speech or communication therapies should be provided, as well as behavioral therapies for autism and individual specialized education plans, if available. Epilepsy management should be based on standard practice depending on the seizure types and EEG findings, acknowledging that tiagabine and vigabatrin are not recommended, and valproate is relatively contraindicated. Notably, the ketogenic diet has not been demonstrated to be of clinical benefit in SSADHD but is not contraindicated. Similarly, no information suggests clinical efficacy from taurine supplementation or other alternative therapies.

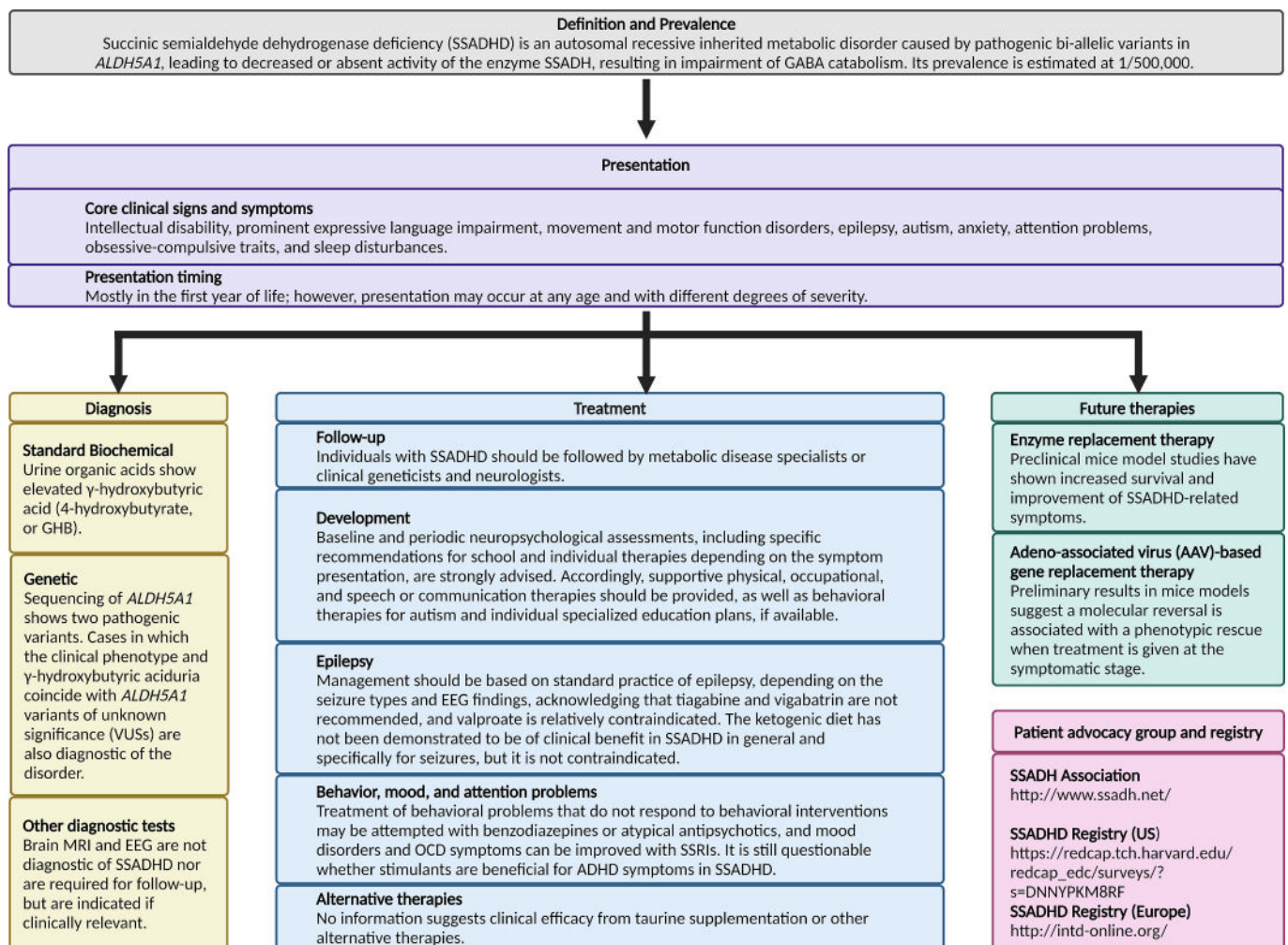


Fig. 3. A flowchart summarizing the succinic semialdehyde dehydrogenase deficiency (SSADHD) Consensus Group recommendations on the definition, epidemiology, clinical presentation, diagnosis, and management of SSADHD.

Treatment of behavioral problems that do not respond to behavioral interventions may be attempted with benzodiazepines or atypical antipsychotics, and mood disorders and OCD symptoms can be improved with SSRIs. It is still questionable whether stimulants are beneficial for ADHD symptoms in SSADHD.

Through ongoing efforts, development of targeted genetic therapies for SSADHD may also provide a more substantial justification for newborn screening for this disorder. Early identification of SSADHD, regardless of phenotypic severity, may presumably prevent the accumulative effects of the hyperGABAergic environment that worsens SSADHD-related symptoms with time, presumably due to years of cerebral excitation:inhibition disbalance.

Given the rarity of SSADHD, there is a certain degree of ambiguity with epidemiological, clinical, diagnostic, and therapeutic aspects of the disorder. The primary aim of constituting these clinical guidelines was to clarify these matters as much as possible and improve the care given to individuals with SSADHD worldwide. As is the case with other rare inherited metabolic disorders, there are inherent challenges to conducting randomized controlled trials, resulting in high-quality evidence in SSADHD. Nevertheless, the consensus guidelines established in this study reflect the best available recommendations provided thus far for SSADHD, predominantly based on expert opinions and the findings from the cohort-based ongoing SSADHD Natural History Study. We encourage caregivers of individuals with SSADHD to join a patient advocacy group, e.g., the SSADH Association (<http://www.ssadh.net/>), and be aware of the SSADHD Registry at the US ([https://redcap.tch.harvard.edu/redcap\\_edc/surveys/?s=DNNYPKM8RF](https://redcap.tch.harvard.edu/redcap_edc/surveys/?s=DNNYPKM8RF)) or European site (<http://intd-onlin.e.org/>).

Future trials should include clinical outcomes as derived from the Externally Led-Patient Focused Drug Development meeting co-sponsored by the FDA and parent advocacy group, specifically speech, communication, intellectual disability, behavioral and psychological symptoms, sleep disturbances, seizures, and physical symptoms [143]. Moreover, future updates of these guidelines will depend on larger and more comprehensive patient outcome data representing longer follow-up investigations.

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### Details of ethics approval

The conduction of this study was approved by the Institutional Review Boards (IRB) of Boston Children's Hospital, Boston, MA, USA (#P00029917).

### Data sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### CRedit authorship contribution statement

**Itay Tokatly Latzer:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Mariarita Bertoldi:** Data curation, Investigation, Methodology, Writing – review & editing. **Nenad Blau:** Data curation, Methodology, Writing – review & editing. **Melissa L. DiBacco:** Data curation, Methodology, Project administration, Writing – review & editing. **Sarah H. Elsea:** Data curation, Investigation, Methodology, Writing – review & editing. **Àngels García-Cazorla:** Data curation, Investigation, Writing – review & editing. **K. Michael Gibson:** Data curation, Funding acquisition, Investigation, Methodology. **Andrea L. Gropman:** Data curation, Investigation, Methodology, Writing – review & editing. **Ellen Hanson:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Carolyn Hoffman:** Conceptualization, Investigation. **Kathrin Jeltsch:** Data curation, Investigation, Methodology, Writing – review & editing. **Natalia Juliá-Palacios:** Data curation, Investigation, Methodology, Writing – review & editing. **Ina Knerr:** Data curation, Investigation, Methodology, Writing – review & editing. **Henry H.C. Lee:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Patrizia Malaspina:** Data curation, Investigation, Methodology, Writing – review & editing. **Alice McConnell:** Data curation, Investigation, Methodology, Writing – review & editing. **Thomas Opladen:** Data curation, Investigation, Methodology, Writing – review & editing. **Mari Oppebøen:** Data curation, Investigation, Methodology, Writing – review & editing. **Alexander Rotenberg:** Data curation, Investigation, Methodology, Writing – review & editing. **Mark Walterfang:** Data curation, Investigation, Methodology, Writing – review & editing. **Lee Wang-Tso:** Data curation, Investigation, Methodology, Writing – review & editing. **Ron A. Wevers:** Data curation, Investigation, Methodology, Writing – review & editing. **Jean-Baptiste Rouillet:** Data curation, Investigation, Methodology, Project administration, Writing – review & editing. **Phillip L. Pearl:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

### Declaration of competing interest

None.

### Data availability

Data will be made available on request.

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