

Review

SUDEP in inherited metabolic epilepsies



Itay Tokatly Latzer ^{a,b}, Charity Adams ^c, Gardiner Lapham ^d, Jeffrey Buchhalter ^e, Phillip L. Pearl ^{a,*}

^a Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

^b School of Medicine, Faculty of Medical and Health Sciences, Tel-Aviv University, Tel Aviv, Israel

^c Parent, Independent Contributor

^d Partners Against Mortality in Epilepsy (PAME), American Epilepsy Society (AES), USA

^e Buchhalter Consulting, Phoenix, AZ, USA

ARTICLE INFO

ABSTRACT

Keywords:

Inborn errors of metabolism
Seizures
Epilepsy
Mortality
Sudden unexpected death

Inherited metabolic epilepsies (IMEs) have an increased susceptibility for early mortality, including sudden unexpected death in epilepsy (SUDEP), as they often manifest with frequent drug-resistant seizures, including bilateral tonic-clonic and nocturnal seizures. The metabolic defects inherent to their etiology predispose affected individuals to an additional risk of mortality as they can lead to brain injury, which can induce and be exacerbated by seizures, and to systemic conditions that decrease seizure-cessation and auto-resuscitation processes. The increased risk for SUDEP in IMEs mandates that special emphasis should be given to identifying them early and attempting to achieve seizure control by managing acute metabolic decompensations, anti-seizure medications, and targeted therapies when available. Providing education and support to individuals with IMEs and their families about SUDEP risk factors and prevention strategies is imperative. Despite the increased risk for SUDEP in IMEs, this topic remains understudied. As a proceeding of the 2024 Partners Against Mortality in Epilepsy (PAME) meeting and aiming to increase awareness, this Review describes the pathophysiological and clinical elements related to the heightened risk of SUDEP in IMEs and provides the perspective of a parent of a child with an IME who died from SUDEP. Calling for action, future research on epilepsy-related mortality in IMEs is required. Investigating this field may also yield insights into the general pathomechanisms of SUDEP.

1. Definitions and Classifications

Inherited metabolic disorders (IMDs), recognized in the past as inborn errors of metabolism, are a group of disorders stemming from various impairments in biochemical metabolic processes. In roughly 20% of the IMDs, seizures are thought to be a predominant manifestation directly affecting the overall outcome [1]. These disorders are designated as Inherited Metabolic Epilepsies (IMEs). Of the several classification approaches to IMEs, the most widely used is the one based on

pathophysiology [2,3]. This broad classification system segregates them into subgroups of small molecule disorders, large molecule disorders, disorders of energy metabolism, and disorders resulting from defects in neurotransmitters, purines and pyrimidines, vitamins, minerals, and heavy metals [4]. As much as their etiologies and pathophysiologies are diverse, so is their clinical presentation. In IMEs presenting earlier in life, manifestations may include lethargy, encephalopathy, respiratory problems, dysmorphism, developmental delays, symmetric motor tone abnormalities, seizures, and death. Later presentations typically

Abbreviations: AADC, Aromatic L-amino acid decarboxylase; AAV, Adeno-associated virus vector; ASMs, Anti-seizure medications; BBB, Blood-brain-barrier; CAD, Carbamoyl phosphate synthetase, aspartate transcarbamylase, and dihydroorotate; CDGs, Congenital disorders of glycosylation; CLN2, Ceroid lipofuscinosis 2; DEEs, Developmental epileptic encephalopathies; EIDEE, Early Infantile Developmental and Epileptic Encephalopathy; GABA, γ -aminobutyric acid; GLUT1, Glucose transporter 1; GPI, Glycosyl phosphatidyl inositol; IMDs, Inherited metabolic disorders; IMEs, Inherited metabolic epilepsies; MSUD, Maple syrup urine disease; PAME, Partners Against Mortality in Epilepsy; PDD-NOS, Pervasive Developmental Disorder – Not Otherwise Specified; PDE, Pyridoxine dependent epilepsy; PKU, Phenylketonuria; PME, Progressive Myoclonus Epilepsy; SSADHD, Succinic semialdehyde dehydrogenase deficiency; SUDEP, Sudden unexpected death in epilepsy.

* Corresponding author at: Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, William G. Lennox Chair and Professor of Neurology, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA.

E-mail addresses: itay.tokatlylatzer@childrens.harvard.edu (I. Tokatly Latzer), charityadams6st@yahoo.com (C. Adams), gardinerlapham@gmail.com (G. Lapham), buchhalter@gmail.com (J. Buchhalter), phillip.pearl@childrens.harvard.edu (P.L. Pearl).

<https://doi.org/10.1016/j.ybeh.2025.110422>

Received 2 March 2025; Received in revised form 25 March 2025; Accepted 11 April 2025

Available online 20 April 2025

1525-5050/© 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

manifest with intellectual and adaptive disabilities, autism spectrum disorder, movement disorders, psychiatric and behavior problems, cardiac, ophthalmic, and endocrine dysfunction, epilepsy, and death. Seizures in IMEs may appear in various forms, onset patterns, and intensities. Those that are more commonly observed include drug-resistant myoclonic, tonic, bilateral tonic-clonic, and atonic seizures, atypical absence seizures, and epilepsy syndromes such as Early Infantile Developmental and Epileptic Encephalopathy (EIDEE), Progressive Myoclonus Epilepsy (PME), Infantile Epileptic Spasms Syndrome, and Lenox-Gastaut Syndrome [5].

Sudden unexpected death in epilepsy (SUDEP) is a devastating complication and the leading cause of death related to epilepsy in children and adults [6]. The overall incidence of SUDEP is reportedly estimated as ~ 1 per 1000 patient-years, and it is marginally lower in the pediatric population [7–10]. “Definite SUDEP” is defined as the “sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in whom post-mortem examination does not reveal a structural or toxicological cause for death.” [11] Cases in which a post-mortem examination is not performed but otherwise meet these criteria are referred to as “probable SUDEP,” and when another potential cause of death is suspected as “possible SUDEP.” The term “SUDEP Plus” reflects cases meeting the criteria of SUDEP in an individual bearing another medical condition that may contribute to mortality [12]. The most significant risk factor for SUDEP is having bilateral tonic-clonic seizures, and the higher their frequency, the higher the risk. Another high-risk factor is having nocturnal seizures [13]. Other important factors linked with an increased risk (yet lower than that of bilateral tonic-clonic and nocturnal seizures) for SUDEP, some of which were specifically studied in pediatric populations, include frequent seizures, non-adherence to anti-seizure medications (ASMs), and pre-and peri-natal complications (being small for gestational age and low Apgar scores) [14–17].

In this Narrative Review, we aim to provide an overview of the interlaced pathophysiological processes of IME mortality and SUDEP, leading to a plausible heightened occurrence rate of SUDEP in IMEs. IME groups and subgroups are discussed separately, focusing on their distinct tenable SUDEP-related pathophysiology, clinical features, and treatments.

2. Mortality in inherited metabolic disorders

Considering IMEs commonly affect multiple organ systems, mortality in IMEs may derive from respiratory (including aspiration pneumonia), cardiac, gastrointestinal, and infectious conditions, as well as neurologic disorders, and it may or may not be related to epilepsy. Existing reports addressing issues related to mortality in IMDs predominantly concentrate on the decreased mortality of IMDs identified through newborn screening programs [18–21]. Investigations not focused on neonatal screening describe that an estimated 0.4–3 % of childhood deaths are caused by IMDs [22,23] and that approximately 25 % of children with IMDs do not survive until adulthood [24]. Other reports on epilepsy-related mortality note an association with neurometabolic conditions; further data on the pathophysiology and role of seizures with comorbidities is needed [6,25,26]. A study examining the long-term follow-up of individuals with IMEs reported four death cases attributed to infectious etiologies in medium-chain acyl-CoA dehydrogenase deficiency, methylmalonic aciduria, and propionic aciduria [20]. Other evidence suggested that respiratory disorders and infections may lead to mortality in many IMEs, including organic acidurias and lysosomal storage diseases [27]. A study of a large cohort of more than one million individuals (up to 14 years of age) described that compared to healthy subjects, those affected by an IMD have a 21-fold risk of death. In the neonatal period, mortality was greatest for disorders of mineral metabolism, e.g., disturbances of calcium or magnesium, and after one year of age, for disorders of sphingolipid metabolism, e.g., Gaucher,

Niemann-Pick, Tay-Sachs disease. Within all the IMDs, the most common causes of mortality were noted to be due to hepatic, gastrointestinal, respiratory, and infectious conditions, and bearing nervous system disorders was also linked to a high mortality risk [28]. This evidence was supported by an 18-year-long population-based study of mortality in rare diseases, reporting that of the IMDs, the lowest survival rates were experienced by individuals with neurologic conditions [29]. Presumably, seizures constituted part of the phenotype of many of the neurological disorders described in these reports. However, there is no specific mention of seizures, epilepsy, or SUDEP in all the studies inspecting the mortality in IMDs. Moreover, detailed descriptions of SUDEP in IMEs are hinted at but not fully deciphered by large cohort studies examining the underlying etiology of SUDEP. A study that focused on the mortality causes of children (up to 18 years of age) with epilepsy admitted to an Epilepsy Center of a tertiary medical center over the course of 10 years (N = 1974) reported that nine subjects (0.45 %) died from probable or possible SUDEP, but none of them had an IME. Of nine other individuals belonging to this cohort who had IMEs and died, deaths were attributed to respiratory insufficiency and various gastrointestinal ailments [30]. Another nationwide case-control study including 78,424 individuals with epilepsy reported that of the 255 cases of SUDEP, two (0.8 %) had metabolic disorders; however, the nature of these disorders was not specified [31].

3. Pathomechanisms of SUDEP

Extensive investigations suggest that the pathomechanisms leading to SUDEP derive from a multifactorial model consisting of cardiac and respiratory system compromise and defects in brainstem arousal processes, denoting a centrally mediated neurological breakdown. In witnessed SUDEP cases, the progression of these failed operations most commonly results in a final occurrence of postictal apnea followed by cardiac arrest [32]. Theories based on impaired metabolism of adenosine and serotonin contributing to SUDEP have also been established in animal models and humans. Adenosine, shown to be released during seizures, is suggested to play an integral role in the seizure-termination mechanism. Yet, adenosine is also known as a respiratory depressant [33–35]. Serotonin, also shown to be released during seizures, possesses a respiratory-enhancing property triggered by the increased post-ictal CO₂ concentrations [36–40]. It is proposed that the actions of serotonin counter the depressive effects of adenosine, and their dual action ensues in seizure termination and autoresuscitation promoted by recovery of respiration [32]. With respect to genetic susceptibility to SUDEP, evidence indicates a polygenic pattern [41]. Genes found to be associated with an increased likelihood of SUDEP encode proteins amenable for neurocardiac and cardiorespiratory functions [42]. For example, seizures may lead to cardiac arrhythmias when occurring in individuals affected by pathogenic variants in SCN1A, SCN2A, SCN8A, SCN1B, GNB5, KCNA1, KCNQ1, DEPD5, and other similar genes encoding for ion or voltage-gated channels expressed in cardiac and cortical tissues [43,44]. Indeed, the SCN1A and SCN8A developmental epileptic encephalopathies (DEEs) are known to be associated with an increased SUDEP risk [45]. This is further supported by findings of a comprehensive exome sequencing analysis, revealing a high rate of SUDEP cases that were found to have genetic variants associated with cardiac arrhythmia (including long QT syndrome) in addition to epilepsy [46]. Other examples of genes with a high SUDEP predisposition include those encoding respiratory control mechanisms, such as PHOX2B, responsible for congenital hypoventilation syndrome [47].

4. The interdependent relationship between metabolic and SUDEP pathomechanisms

The first and foremost reason for a presumed increased SUDEP risk in IMEs is that most of them are associated with frequent drug-resistant seizures, including bilateral tonic-clonic and nocturnal seizures [13].

However, other important factors rooted in the metabolic pathomechanisms of IMEs may increase the predisposition to SUDEP in affected individuals. This increased risk is embodied by a combination of factors and their interaction: abundant drug-resistant seizures induced by biochemical metabolic impairments, additional seizure-induced exacerbation of existing brain injury (derived from the metabolic disorder), and underlying systemic problems that hinder the ability of restorative respiration and aggravate the sequence of events terminated by cardiac arrest (Fig. 1). The subsequent segments detail the pathophysiological and clinical attributes of selected individual IMEs representing each of the IME groups [2], which are relevant within the context of SUDEP. Considering the wide gamut of IMEs, we concentrated on those in which epilepsy is typically drug-resistant and characterized by multiple types of seizures, including bilateral tonic-clonic. Table 1 presents a broader scope of IMEs within this framework.

4.1. Small molecule disorders

4.1.1. Aminoacidemias

Maple syrup urine disease (MSUD) results from a branched-chain α -ketoacid dehydrogenase (BCKDH) complex deficiency. This ensues in a buildup of branched-chain amino acids (as may be revealed in a quantitative plasma amino acid analysis) and α -ketoacids (as may be observed in a urine organic acids analysis), leading to interference with the blood-brain-barrier (BBB), which may contribute to acute encephalopathy and brain edema [48]. Concurrent seizures may further disrupt the BBB, increasing the buildup of other toxic substances (α -ketoisocaproic acid) and exacerbating cytotoxic edema. Hence, in individuals with MSUD, it is plausible that a seizure may trigger or worsen a fatal cascade of metabolic events. [49].

4.1.2. Organic acidurias

Propionic acidemia is an autosomal recessive disorder caused by a deficiency of the biotin-dependent propionyl-CoA carboxylase. This leads to an impaired conversion of propionyl-CoA to d-methylmalonyl-

CoA, disrupting the breakdown of several amino and fatty acids. Urine organic acid analysis reveals elevated levels of 3-hydroxypropionate, methylcitrate, propionylglycine, and tiglylglycine. Other metabolic screening tests may show an increased anion gap metabolic acidosis and hyperammonemia [50]. In addition to various types of generalized seizures (including bilateral tonic-clonic), cardiac ailments are also common in this disorder, including cardiomyopathy and an acquired long-QT syndrome [51]. Seizures occurring in individuals with a phenotype including severe myocardial involvement may lead to SUDEP as part of an exacerbated cardiac decompensation and acute heart failure [52,53].

4.1.3. Urea cycle disorders (UCDs)

represent a group of disorders resulting from partial or complete deficiencies of enzymes amenable for removal of nitrogenous waste. All of the UCDs are inherited in an autosomal recessive manner, except for ornithine transcarbamylase deficiency, in which it is X-linked dominant. If untreated, the increasing levels of ammonia lead to hyperammonemic encephalopathy, associated with severe cerebral edema and increased intracranial pressure, which can result in brain herniation and death [54]. As most of the neurological manifestations associated with UCDs, seizures can result from the hyperammonemic crises. They can evolve into status epilepticus and can exacerbate the encephalopathy and life-threatening neurologic sequela [55]. Importantly, seizures in UCDs may be subclinical [56,57], further emphasizing the need to monitor for early clinical signs of hyperammonemia (e.g., confusion, lethargy) and treat it aggressively once recognized, as part of SUDEP prevention in UCDs [58].

4.2. Large molecule disorders

4.2.1. Lysosomal storage disease

Gaucher type III is caused by pathogenic variants in the gene encoding acid β -glucuronidase, resulting in the accumulation of glucosylceramide. Of the three types of Gaucher, type III is associated with the worst neurologic manifestations and outcomes. Seizure types in this disorder

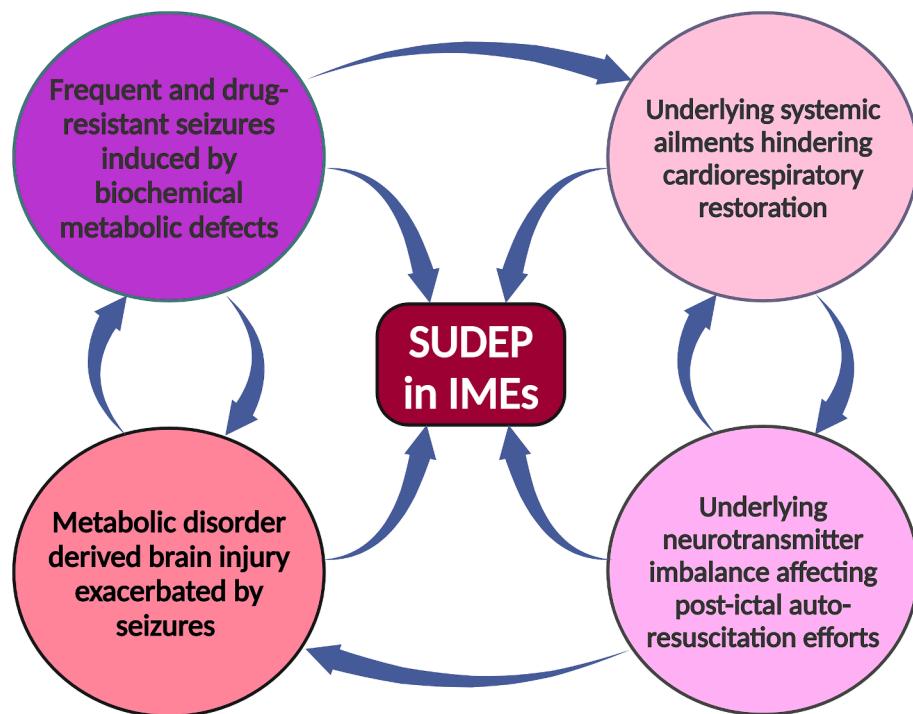


Fig. 1. The interdependent relationship between characteristics of inherited metabolic epilepsies (IMEs) that increase their risk for sudden unexpected death in epilepsy (SUDEP): abundant drug-resistant seizures induced by biochemical metabolic impairments and underlying systemic and neurotransmitter-related problems hindering restorative respiration and aggravating the sequence of events culminating in cardiac arrest and death.

Table 1

Examples of pathophysiologic and clinical features of IMEs that may account for an increased risk for SUDEP.

Pathophysiology and clinical characteristics associated with an increased SUDEP risk		Inherited metabolic epilepsies
Intrinsic SUDEP risk factors	Drug-resistant epilepsy, including bilateral tonic-clonic seizures	Of the ~ 250 inherited metabolic epilepsies, ~80 % are regarded as drug-resistant, most of which can also present with bilateral tonic-clonic seizures [1]
Metabolic disturbances derived refractory seizures and status epilepticus, among other brain injuries	Metabolic acidosis	Organic acidemias; urea cycle disorders; mitochondrial disorders; fatty acid oxidation disorders
Cytotoxic brain edema derived from altered blood-brain-barrier	Hyperammonemia	Urea cycle disorders; organic acidemias Maple syrup urine disease
Underlying cardiac conditions hindering post-ictal cardiac restoration	Accumulated branched chain amino acids and toxic compounds (e.g., α-ketoisocaproic acid)	Propionic acidemia, NCL2 disease, CPT2 deficiency, mitochondrial inorganic pyrophosphatase deficiency
	Cardiac arrhythmia	Propionic acidemia, D-2-hydroxyglutaric aciduria type 2, CDG-DOLK, CDG-PGM1, mitochondrial diseases
	Dilated cardiomyopathy	Gaucher disease type III CDG-PMM2
	Valvulopathy	Cystathione beta-synthase deficiency, Menkes disease
	Hypertrophic cardiomyopathy	Mitochondrial diseases (most notably in complex IV subunits, TCA-cycle disorders, disorders of mitochondrial carriers, and disorders of mitochondrial cofactor biosynthesis); peroxisomal biosynthesis disorders; CDGs
	Vasculopathy	Urea cycle disorders; Zellweger syndrome, Mitochondrial diseases, CDGs, peroxisomal biosynthesis disorders, aminoacidopathies
Underlying respiratory conditions impeding post-ictal auto-resuscitation efforts	Respiratory failure	Methylmalonic acidemia; homocystinuria (Cbl-C type)
	Apnea	Aromatic L-amino acid decarboxylase (AADC); disorders of tetrahydrobiopterin (BH4); SSADHD (serotonin may be affected secondary to increased GABA levels)
	Predisposition to airway aspiration	
	Cor pulmonale	
Impaired ability of respiratory enhancement triggered by the increased post-ictal CO ₂ concentrations	Alteration of serotonin levels	

[1] Tokatly Latzer I, Blau N, Ferreira CR, Pearl PL. Clinical and biochemical footprints of inherited metabolic diseases. XV. Epilepsies. Mol Genet Metab 2023;140: 107690.

AADC- aromatic L-amino acid decarboxylase; CDGs- congenital disorders of glycosylation; CO₂- carbon dioxide; CPT2- carnitine palmitoyltransferase 2; GABA- gamma aminobutyric acid; NCL2- neuronal ceroid lipofuscinoses 2; SUDEP- sudden unexpected death in epilepsy; TCA- tricarboxylic acid.

may be focal or generalized, including myoclonic and bilateral tonic-clonic [59]. In a study describing the sudden death of 12 individuals with Gaucher type III, the majority had died after a seizure, and their deaths were attributed to SUDEP. Interestingly, the EEG of more than half of them had been normal prior to their SUDEP [60]. The risk for

SUDEP in this population may also be linked to their hindered ability of auto-resuscitative measures due to underlying cardiac-related conditions [61]. Moreover, the phenotype of Gaucher type IIIc specifically includes cardiac valvulopathies in the form of aortic and mitral valve calcification, leading to stenosis and regurgitation [62].

4.2.2 Congenital disorders of glycosylation (CDGs) represent a group of multisystemic disorders derived from impairment of glycosylation of *N* and *O*-linked glycoproteins and glycolipids. The abnormal glycoforms associated with CDGs can be detected by transferrin isoelectric analysis, although nowadays genetic tests are primarily used for their diagnosis [63]. A diverse spectrum of seizure types constitutes part of the multisystemic manifestations characterizing CDGs, which also include hepatopathy, hypoglycemia, protein-losing enteropathy, cardiomyopathy, pulmonary diseases, and immunologic deficiencies [63]. The many underlying systemic conditions in CGDs may predispose affected individuals to post-ictal cardiorespiratory failure derived from their inherent low cardiac output. In a report describing high early mortality (30 %) in CDG-PIGA, 10 % of deaths were attributed to possible SUDEP (autopsies were not performed routinely, and the definite cause of death remained unidentified in most cases) [64]. SUDEP in individuals with glycosyl phosphatidyl inositol (GPI) deficiency, a subgroup of CDGs, has also been reported [65].

4.3. Disorders of energy metabolism

Mitochondrial diseases comprise a large and heterogeneous group of disorders in which cellular energy production is impaired, as well as other vital molecular functions, such as apoptosis initiation and reactive oxygen species removal. These diseases are characterized by multisystemic and neurological manifestations. Epilepsy is common but not universal for mitochondrial diseases and may feature any seizure type and status epilepticus [66]. Seizures in mitochondrial diseases may exacerbate existing disturbed cerebral energy production, worsening the decompensation and recovery ability. They may also lead to secondary complications such as intracerebral bleeding, exacerbating the brain injury [67]. Cardiopulmonary failure, aspiration pneumonia, pulmonary embolism, renal failure, and status epilepticus have accounted for deaths in individuals with mitochondrial diseases. Unexpected death has been reported for a third of cases. However, similar to other disorders with multisystemic involvement, it is challenging to determine the precise etiology in many of these cases, and definite or probable SUDEP is infrequently described in mitochondrial conditions [68].

4.4. Disorders of neurotransmitters

Succinic semialdehyde dehydrogenase deficiency (SSADHD)-

One notable example of SUDEP in a neurotransmitter disorder is provided by SSADHD, a disorder characterized by γ-aminobutyric acid (GABA) accumulation. Approximately half of the individuals with SSADHD experience seizures, which tend to emerge and worsen around early adolescence [69]. Seizures occurring in SSADHD may be regarded as “paradoxical” since this disorder is characterized by hyperphysiologic levels of GABA, the primary cortical inhibitory neurotransmitter [70]. However, it has been postulated that with time, the accumulated GABA leads to the downregulation of GABA receptors [71], possibly reducing the inhibitory effect and further disrupting cerebral cortical excitatory: inhibitory balance. In adults with SSADHD, SUDEP has been shown to occur at a high rate of nearly 15 % [72]. The increased GABA concentrations may also negatively impact serotonin metabolism [73]. When disturbed, serotonin-dependent post-ictal respiratory auto-resuscitation mechanisms may be flawed [74,75], and SUDEP may occur. The Parent Perspective of an adolescent boy with SSADHD who died from SUDEP is provided below (Box 1, Fig. 2).

Box 1

Parent's Perspective.

Blissful delirium aptly described my emotional response to the invitation to share the story of the events that forever changed my family. Let me first introduce my gorgeous party of three. I am Charity, a contented American mummy, wife, and author. In 2004, my Australian husband, Steven, and I chose to call Dubai home before welcoming our beloved son, Bond Walter Toohey (Fig. 2A). Bond was an easy-going baby, happily engaging in the world around him, but developmental delays were evident, and by age two, our excuses had worn thin. A well-intentioned doctor diagnosed him with high-functioning autism, or PDD-NOS (Pervasive Developmental Disorder- Not Otherwise Specified)- the first acronym to define our lives. Unconvinced, we stayed focused on elevating Bond beyond his limitations. Through intensive therapies, he made substantial progress but continued to struggle with a severe language delay. Although we sought advice from doctors across the globe, it was a visiting pediatric neurologist in Dubai who, upon meeting nine-year-old Bond, immediately suspected an inherited metabolic disorder and expressed frustration for the lazy autism diagnosis. A simple urine test gave weight to his inclinations, and DNA sequencing confirmed them: Succinic Semialdehyde Dehydrogenase Deficiency – let's just go with our second acronym, SSADHD. We were now part of an ultra-rare disease family whose global numbers only total 350. Bond presented with several symptoms like expressive language and intellectual delays, but there was one glaring box we did not tick: epilepsy. This was true until the discombobulating throws of puberty decided otherwise.

It was an early morning in a quiet corner of Thailand. Steven shook me awake; Bond was frozen by a tonic seizure. When a second, this time a bilateral tonic-clonic seizure, arrived a month later, we placed our hopes in medicine. Sadly, the first anti-seizure medication only managed to turn him into the Incredible Hulk, and while others gave us back our darling boy, none were able to control the seizures. A seizure monitoring watch provided the independence teenage Bond craved, but his epilepsy refused to be tamed. Bond became the first participant in the groundbreaking SSADHD Natural History Study. For his copious contributions of data and, I am assuming, entertainment, he was bestowed the title “Trailblazer” (Fig. 2B). Recollecting this endearing moniker tops up my blissful delirium reserves.

Among the many conversations we had with Dr. Pearl, the principal investigator of the study, he gently mentioned that sudden unexpected death in epilepsy, although rare, was more common with our disease. He spoke in a way not to cause alarm, so I filed the information away, until three months later, at the start of the school holidays, when I went to wake my sleepy boy for his morning meds. As emergency swirled, Dr. Pearl's words kept panic at bay, affording me clarity to ruminate on Bond's final sentiments when kissing goodnight, “Luv 'ew Gaggy, Luv 'ew Mummy.” Even after five years, I grapple daily with a petulant brain, surmising ways I could have saved Bond. With a deep breath and a bit of self-praise for still being a good mum, Dr. Pearl's words continue to provide solace, reaffirming there was nothing I could have done to prevent SUDEP, that final acronym defining our lives.

Because of resolute doctors, teachers, therapists, and loved ones, Bond had become a confident, happy teenager, living in partnership with an ultra-rare disease (Fig. 2, C and D).

Now, it is Steven and I who are learning to live with an unwelcome partnership – that of grief. Ending our story with such sorrow would be a disservice to our happy Bond, and in turn, we would love to share a memory that perfectly captures his life.

We were one of the first families living in a new community, and for Bond, this meant Goonies-type adventures, exploring the desolate streets and winding footpaths. I was comfortable with his two-wheeled explorations if he stopped every few laps to check-in. His cheeky interpretation – whizzing past the garden gate yelling, “Hi, Mummy!” One exceptionally beautiful day when the sky felt infinitely blue, I walked outside and caught a glimpse of Bond standing on his bike pedals, eyes closed, basking towards the warm sun. His broad, contented smile said it all; he had found freedom – which, in youth, your bicycle can provide. Mesmerized, I watched him peddle into his next lap before my mummy brain clicked, “That boy was cycling with his eyes closed!” It was a moment of revelry for me, but for our Bond, this is how he lived every day of his short life – deeply present, guided by an internal compass of pure happiness.

4.5. Vitamin-related disorders

Pyridoxine-dependent epilepsy is caused by pathogenic variants in *ALDH7A1* encoding for antiquitin, which is involved in the degradation of lysine [76]. Additionally, pyridoxine has a fundamental role in the synthesis of several neurotransmitters, including serotonin, dopamine, epinephrine, norepinephrine, and GABA, also through reactions involving the enzyme aromatic amino acid decarboxylase, which is dependent on pyridoxal 5-phosphate [77]. The mainstay treatment for PDE is pyridoxine. Other forms of the disorder may be treated with folic acid or pyridoxal 5-phosphate [78]. However, if left untreated, seizures intensify and culminate in super refractory status epilepticus [77]. SUDEP in PDE may be linked to prolonged seizure activity and associated brain damage, respiratory distress, and cardiovascular collapse [79]. It is possible that the reduced serotonin levels facilitated by the inherent metabolic defect of the disorder also impede the postictal auto-resuscitation efforts [80].

5. Prevention of SUDEP in inherited metabolic epilepsies

The plausible high risk for SUDEP in IMEs underscores the importance of seizure management in affected individuals. Metabolic decompensations should be treated acutely, focusing on negating

intoxications, addressing intercurrent infections, and correcting hypoglycemia and electrolyte disturbances [4]. The currently available chronic treatment strategies for many IMEs are only supportive, and seizures are managed with anti-seizure medications as per the standard of care in epilepsy. However, an estimated 20 % of IMEs have disease-specific treatments targeting their metabolic defects that can mitigate or lead to cessation of seizures and improve neurodevelopmental outcomes [81]. For this reason, early identification of IMEs is imperative, especially if done at a young age, as some of these targeted treatments are most efficacious if administered as early as possible in the disease course. These treatments range from accessible and affordable dietary regimens to complex genetic therapies [82]. Notable examples include the modified low-phenylalanine and low-protein diet as well as tyrosine supplementation for phenylketonuria (PKU) [83], the pyrimidine uridine for CAD (carbamoyl phosphate synthetase, aspartate transcarbamylase, and dihydroorotate) deficiency [84], cerliponase alfa, a recombinant human TPP1 proto-enzyme, introduced intraventricularly, for ceroid lipofuscinosis 2 (CLN2) [85], the ketogenic diet for glucose transporter 1 (GLUT1) deficiency [86], biotin for biotinidase deficiency [87], vitamin B6 for pyridoxine dependent epilepsy (PDE) [88], and even more recently intra-putamenally injected adeno-associated virus vector (AAV) gene therapy eladocagene exuparvovec for aromatic L-amino acid decarboxylase (AADC) deficiency [89]. In addition to seizure

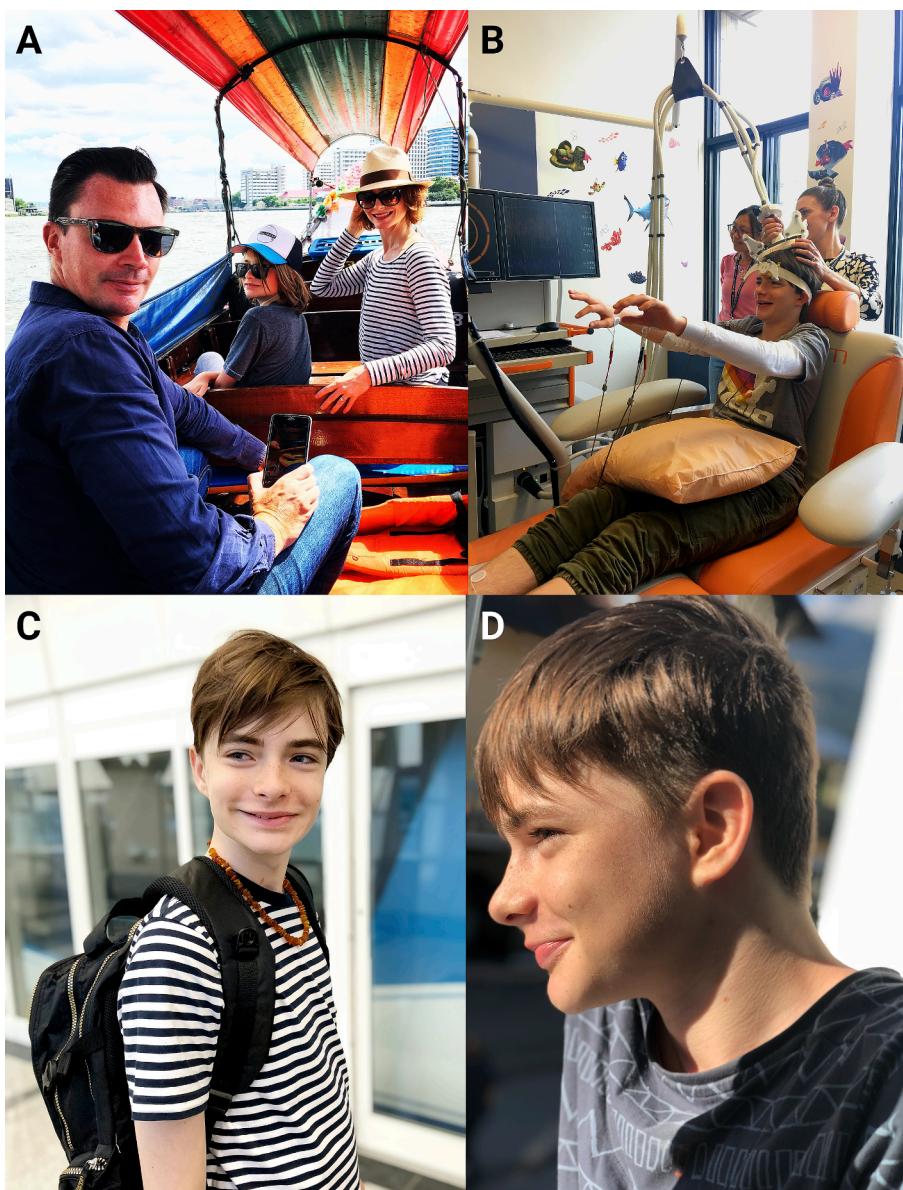


Fig. 2. Bond Walter Toohey, a boy with succinic semialdehyde dehydrogenase deficiency (SSADHD) who died from SUDEP.

control with ASMs or targeted therapies, general recommendations of SUDEP prevention should be emphasized and implemented for individuals with IMEs, including avoidance of seizure triggers, seizure monitoring, ASM compliance, nocturnal supervision or a listening device, avoiding sleeping in the prone position, and airway protection. All individuals with epilepsy and their caregivers should receive counseling regarding sudden SUDEP [90,91] and the importance of adhering to its preventative measures [92], with particular emphasis for those at elevated risk, as is the case for many individuals with IMEs. Due to the diverse medical complexities that may draw the focus in individuals with IMEs and limited research on SUDEP in this context, it is possible that SUDEP may not be thoroughly discussed in this population as it should be. Further studies are needed to explore and raise awareness of this risk.

There are several important learnings that can be gleaned from the experience of the parents of the young man who succumbed to SUDEP in the context of SSADHD (Box 1, Fig. 1). The first is that they were informed about the possibility of SUDEP by the treating neurologist. In addition, the opportunity to prevent SUDEP through aggressive anti-seizure treatment was pursued. Next, IMEs are a heterogeneous group of

disorders with a range of disease course. In the instance noted, the patient did not develop seizures until later in childhood at which treatment was sought, demonstrating that the possibility of SUDEP is present at some time after the diagnosis.

6. Conclusions

Inherited metabolic epilepsies (IMEs) reflect the inherited metabolic disorders in which seizures are a predominant and outcome-determining clinical component. Individuals with IMEs possess the main risk factors for the devastating occurrence of SUDEP: frequent drug-resistant seizures, including bilateral tonic-clonic and nocturnal seizures. Additionally, they often present with other SUDEP risks, such as intellectual disability and an abnormal neurologic examination. The risk for SUDEP is further increased in IMEs as their inherent metabolic impairments predispose affected individuals to brain injury, which can both elicit and be exacerbated by seizures, and systemic ailments that diminish the seizure-cessation and auto-resuscitation mechanisms. Early identification and seizure management of IMEs is further stressed by the notion that they are prone to an increased SUDEP risk. However, this Review

found a dearth of evidence to indicate the real incidence of SUDEP in IMEs. Thus, research is required to ascertain in which IMEs SUDEP may occur and the effect of aggressive treatment on longevity. Additionally, it is crucial to identify and manage other factors that may contribute to early mortality in IMEs, such as cerebrovascular accidents, cerebral edema, and cardiac and respiratory abnormalities. Finally, providing education and support to individuals with IMEs and their families can help them recognize and respond to the signs of SUDEP. Despite the increased risk for SUDEP in this population, this topic remains under-described and –appreciated. As a proceeding of the 2024 Partners Against Mortality in Epilepsy (PAME) meeting, we emphasize pathophysiological and clinical aspects of SUDEP in inherited metabolic epilepsies and call for action and future research of epilepsy-related mortality in this unique group of disorders. Investigations of this field may not only allow a better understanding of the processes and prevention strategies of SUDEP in IMEs; they may yield insights into the general pathomechanisms of SUDEP.

Funding.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Itay Tokatly Latzer: Writing – original draft, Conceptualization. **Charity Adams:** Writing – original draft. **Gardiner Lapham:** Writing – review & editing. **Jeffrey Buchhalter:** Writing – review & editing, Conceptualization. **Phillip L. Pearl:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Tokatly Latzer I, Blau N, Ferreira CR, Pearl PL. Clinical and biochemical footprints of inherited metabolic diseases. XV Epilepsies Mol Genet Metab 2023;140:107690.
- [2] Ferreira CR, Rahman S, Keller M, Zschocke J. An international classification of inherited metabolic disorders (ICIMD). *J Inher Metab Dis* 2021;44:164–77.
- [3] Saudubray JM, Mochel F, Lamari F, Garcia-Cazorla A. Proposal for a simplified classification of IMB based on a pathophysiological approach: A practical guide for clinicians. *J Inher Metab Dis* 2019;42:706–27.
- [4] Saudubray JM, Garcia-Cazorla A. Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management. *Pediatr Clin North Am* 2018;65:179–208.
- [5] Zuberi SM, Wirrell E, Yozawitz E, Wilmhurst JM, Specchio N, Riney K, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia* 2022;63:1349–97.
- [6] Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 2010;363:2522–9.
- [7] Tomson T, Andersson T, Carlsson S, Sveinsson O. Influence of Risk Factor Combinations on Incidence Rates of SUDEP: A Population-Based Study. *Neurology* 2025;104:e213372.
- [8] Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2017;88:1674–80.
- [9] Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. *Neurology* 2017;89:170–7.
- [10] Keller AE, Whitney R, Li SA, Pollanen MS, Donner EJ. Incidence of sudden unexpected death in epilepsy in children is similar to adults. *Neurology* 2018;91:e107–11.
- [11] Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia* 2012;53:227–33.
- [12] Shankar R, Donner EJ, McLean B, Nashef L, Tomson T. Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. *Epileptic Disord* 2017;19:1–9.
- [13] Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. *Neurology* 2020;94:e419–29.
- [14] Whitney R, Sharma S, Ramachandranair R. Sudden unexpected death in epilepsy in children. *Dev Med Child Neurol* 2023;65:1150–6.
- [15] Abdel-Mannan O, Taylor H, Donner EJ, Sutcliffe AG. A systematic review of sudden unexpected death in epilepsy (SUDEP) in childhood. *Epilepsy Behav* 2019;90:99–106.
- [16] Verducci C, Hussain F, Donner E, Moseley BD, Buchhalter J, Hesdorffer D, et al. SUDEP in the North American SUDEP Registry: The full spectrum of epilepsies. *Neurology* 2019;93:e227–36.
- [17] Sveinsson O, Andersson T, Carlsson S, Tomson T. Perinatal risk factors for SUDEP: A population-based case-control study. *Epilepsia* 2022;63:e119–24.
- [18] Frazier D, Millington D, McCandless S, Koeberl D, Weavil S, Chaing S, et al. The tandem mass spectrometry newborn screening experience in North Carolina: 1997–2005. *Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism* 2006;29:76–85.
- [19] Landau YE, Waisbren SE, Chan LM, Levy HL. Long-term outcome of expanded newborn screening at Boston children's hospital: benefits and challenges in defining true disease. *J Inher Metab Dis* 2017;40:209–18.
- [20] Couce ML, Castiñeiras DE, Bóveda MD, Baña A, Cocho JA, Iglesias AJ, et al. Evaluation and long-term follow-up of infants with inborn errors of metabolism identified in an expanded screening programme. *Mol Genet Metab* 2011;104:470–5.
- [21] Wilcken B, Haas M, Joy P, Wiley V, Bowling F, Carpenter K, et al. Expanded newborn screening: outcome in screened and unscreened patients at age 6 years. *Pediatrics* 2009;124:e241–8.
- [22] Goel H, Lusher A, Boneh A. Pediatric mortality due to inborn errors of metabolism in Victoria, Australia: a population-based study. *JAMA* 2010;304:1070–2.
- [23] Waters D, Adeloye D, Woolham D, Wastnedge E, Patel S, Rudan I. Global birth prevalence and mortality from inborn errors of metabolism: a systematic analysis of the evidence. *J Glob Health* 2018;8.
- [24] Dionisi-Vici C, Rizzo C, Burlina AB, Caruso U, Sabetta G, Uziel G, et al. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. *J Pediatr* 2002;140:321–9.
- [25] Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: A call for action. *Neurology* 2016;86:779–86.
- [26] Donner EJ, Camfield P, Brooks L, Buchhalter J, Camfield C, Loddemkemper T, et al. Understanding Death in Children With Epilepsy. *Pediatr Neurol* 2017;70:7–15.
- [27] Santamaría F, Montella S, Mirra V, De Stefano S, Andria G, Parenti G. Respiratory manifestations in patients with inherited metabolic diseases. *Eur Respir Rev* 2013;22:437–53.
- [28] Auger N, Nelson C, Brousseau É, Bilodeau-Bertrand M, Dewar R, Arbour L. Extended risk of mortality in children with inborn errors of metabolism: a longitudinal cohort study. *J Pediatr* 2023;252(16–21):e2.
- [29] Mazzucato M, Visonà Dalla Pozza L, Minichiello C, Toto E, Vianello A, Facchini P, et al. through 2019. *Orphanet J Rare Dis* 2002;2023(18):362.
- [30] Grønborg S, Uldall P. Mortality and causes of death in children referred to a tertiary epilepsy center. *Eur J Paediatr Neurol* 2014;18:66–71.
- [31] Sveinsson O, Andersson T, Carlsson S, Tomson T. Type, Etiology, and Duration of Epilepsy as Risk Factors for SUDEP: Further Analyses of a Population-Based Case-Control Study. *Neurology* 2023;101:e2257–65.
- [32] Faingold CL, Feng HJ. A unified hypothesis of SUDEP: Seizure-induced respiratory depression induced by adenosine may lead to SUDEP but can be prevented by autoresuscitation and other restorative respiratory response mechanisms mediated by the action of serotonin on the periaqueductal gray. *Epilepsia* 2023;64:779–96.
- [33] Van Gompel JJ, Bower MR, Worrell GA, Stead M, Chang SY, Goerss SJ, et al. Increased cortical extracellular adenosine correlates with seizure termination. *Epilepsia* 2014;55:233–44.
- [34] Boison D. Adenosine dysfunction in epilepsy. *Glia* 2012;60:1234–43.
- [35] Shen HY, Li T, Boison D. A novel mouse model for sudden unexpected death in epilepsy (SUDEP): role of impaired adenosine clearance. *Epilepsia* 2010;51:465–8.
- [36] Richter DW, Manzke T, Wilken B, Ponimaskin E. Serotonin receptors: guardians of stable breathing. *Trends Mol Med* 2003;9:542–8.
- [37] Richter DW, Smith JC. Respiratory rhythm generation in vivo. *Physiology* 2014;29:58–71.
- [38] Cheng H-m, Gao C-s, Lou Q-w, Chen Z, Wang Y. The diverse role of the raphe 5-HTergic systems in epilepsy. *Acta Pharmacol Sin* 2022;43:2777–88.
- [39] Kouchi H, Ogier M, Dieuset G, Morales A, Georges B, Rouanet J-L, et al. Respiratory dysfunction in two rodent models of chronic epilepsy and acute seizures and its link with the brainstem serotonin system. *Sci Rep* 2022;12:10248.
- [40] Petrucci AN, Joyal KG, Purnell BS, Buchanan GF. Serotonin and sudden unexpected death in epilepsy. *Exp Neurol* 2020;325:113145.
- [41] Leu C, Balestrini S, Maher B, Hernández-Hernández L, Gormley P, Hämäläinen E, et al. Genome-wide polygenic burden of rare deleterious variants in sudden unexpected death in epilepsy. *EBioMedicine* 2015;2:1063–70.
- [42] Manolis TA, Manolis AA, Melita H, Manolis AS. Sudden unexpected death in epilepsy: The neuro-cardio-respiratory connection. *Seizure* 2019;64:65–73.
- [43] Bagnall RD, Ingles J, Yeates L, Berkovic SF, Semsharian C. Exome sequencing-based molecular autopsy of formalin-fixed paraffin-embedded tissue after sudden death. *Genet Med* 2017;19:1127–33.
- [44] Sahly AN, Shevell M, Sadleir LG, Myers KA. SUDEP risk and autonomic dysfunction in genetic epilepsies. *Auton Neurosci* 2022;237:102907.
- [45] Coll M, Oliva A, Grassi S, Brugada R, Campuzano O. Update on the genetic basis of sudden unexpected death in epilepsy. *Int J Mol Sci* 2019;20:1979.
- [46] Bagnall RD, Crompton DE, Petrovski S, Lam L, Cutmore C, Garry SI, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. *Ann Neurol* 2016;79:522–34.

- [47] Bagnall RD, Crompton DE, Cutmore C, Regan BM, Berkovic SF, Scheffer IE, et al. Genetic analysis of PHOX2B in sudden unexpected death in epilepsy cases. *Neurology* 2014;83:1018–21.
- [48] Strauss KA, Carson VJ, Soltys K, Young ME, Bowser LF, Puffenberger EG, et al. Branched-chain alpha-ketoacid dehydrogenase deficiency (maple syrup urine disease): Treatment, biomarkers, and outcomes. *Mol Genet Metab* 2020;129:193–206.
- [49] Riville Jr JJ, Rezvani I, DiGeorge AM, Foley CM. Cerebral edema causing death in children with maple syrup urine disease. *J Pediatr* 1991;119:42–5.
- [50] Pena L, Franks J, Chapman KA, Gropman A, Ah Mew N, Chakrapani A, et al. Natural history of propionic acidemia. *Mol Genet Metab* 2012;105:5–9.
- [51] Kovacevic A, Garbade SF, Hörster F, Hoffmann GF, Gorenflo M, Merle D, et al. Detection of early cardiac disease manifestation in propionic acidemia - Results of a monocentric cross-sectional study. *Mol Genet Metab* 2022;137:349–58.
- [52] Baumgartner D, Scholl-Bürgi S, Sass JO, Sperl W, Schweigmann U, Stein JI, et al. Prolonged QTc intervals and decreased left ventricular contractility in patients with propionic acidemia. *J Pediatr* 2007;150(192–7):197.e1.
- [53] Mardach R, Verity MA, Cederbaum SD. Clinical, pathological, and biochemical studies in a patient with propionic acidemia and fatal cardiomyopathy. *Mol Genet Metab* 2005;85:286–90.
- [54] Summar ML, Dobbelare D, Brusilow S, Lee B. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. *Acta Paediatr* 2008;97:1420–5.
- [55] Beddoes P, Nerone G, Tai C. Status epilepticus secondary to hyperammonaemia: a late presentation of an undiagnosed urea cycle defect. *BMJ Case Rep* 2021;2021:14.
- [56] Sen K, Whitehead M, Castillo Pinto C, Caldovic L, Gropman A. Fifteen years of urea cycle disorders brain research: Looking back, looking forward. *Anal Biochem* 2022;636:114343.
- [57] Batshaw ML, Tuchman M, Summar M, Seminara J. A longitudinal study of urea cycle disorders. *Mol Genet Metab* 2014;113:127–30.
- [58] Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis* 2012;7:32.
- [59] Schwartz IVD, Göker-Alpan Ö, Kishnani PS, Zimran A, Renault L, Panahloo Z, et al. Characteristics of 26 patients with type 3 Gaucher disease: A descriptive analysis from the Gaucher Outcome Survey. *Mol Genet Metab Rep* 2018;14:73–9.
- [60] Abdelwahab M, Blankenship D, Schiffmann R. Long-term follow-up and sudden unexpected death in Gaucher disease type 3 in Egypt. *Neurol Genet* 2016;2:e55.
- [61] Grabowski GA, Kishnani PS, Alcalay RN, Prakalapakorn SG, Rosenbloom BE, Tuason DA, et al. Challenges in Gaucher disease: Perspectives from an expert panel. *Mol Genet Metab* 2025;145:109074.
- [62] Ferreira CR, Blau N. Clinical and biochemical footprints of inherited metabolic diseases. IV. Metabolic cardiovascular disease. *Mol Genet Metab* 2021;132:112–8.
- [63] Ondruskova N, Cechova A, Hanskova H, Honzik T, Jaeken J. Congenital disorders of glycosylation: Still “hot” in 2020. *Biochim Biophys Acta Gen Subj* 2021;1865:129751.
- [64] Bayat A, Kløvgaard M, Johannessen KM, Barakat TS, Kievit A, Montomoli M, et al. Deciphering the premature mortality in PIGA-CDG - An untold story. *Epilepsy Res* 2021;170:106530.
- [65] Sidpra J, Sudhakar S, Biswas A, Massey F, Turchetti V, Lau T, et al. The clinical and genetic spectrum of inherited glycosylphosphatidylinositol deficiency disorders. *Brain* 2024;147:2775–90.
- [66] Lim A, Thomas RH. The mitochondrial epilepsies. *Eur J Paediatr Neurol* 2020;24:47–52.
- [67] Finsterer J, Zarrouk MS. Epilepsy in mitochondrial disorders. *Seizure* 2012;21:316–21.
- [68] Eom S, Lee HN, Lee S, Kang HC, Lee JS, Kim HD, et al. Cause of Death in Children With Mitochondrial Diseases. *Pediatr Neurol* 2017;66:82–8.
- [69] Tokatly Latzer I, Roullet J-B, Afshar-Saber W, Lee HH, Bertoldi M, McGinty GE, et al. Clinical and molecular outcomes from the 5-Year natural history study of SSADH Deficiency, a model metabolic neurodevelopmental disorder. *J Neurodev Disord* 2024;16:21.
- [70] Tokatly Latzer I, Bertoldi M, DiBacco ML, Arning E, Tsuboyama M, MacMullin P, et al. The presence and severity of epilepsy coincide with reduced γ -aminobutyrate and cortical excitatory markers in succinic semialdehyde dehydrogenase deficiency. *Epilepsia* 2023;64:1516–26.
- [71] Pearl PL, Gibson KM, Quezado Z, Dustin I, Taylor J, Trzcienski S, et al. Decreased GABA-A binding on FMZ-PET in succinic semialdehyde dehydrogenase deficiency. *Neurology* 2009;73:423–9.
- [72] DiBacco ML, Pop A, Salomons GS, Hanson E, Roullet JB, Gibson KM, et al. Novel ALDH5A1 variants and genotype: Phenotype correlation in SSADH deficiency. *Neurology* 2020;95:e2675–82.
- [73] Tao R, Auerbach SB. Regulation of serotonin release by GABA and excitatory amino acids. *J Psychopharmacol* 2000;14:100–13.
- [74] Richerson GB, Buchanan GF. The serotonin axis: Shared mechanisms in seizures, depression, and SUDEP. *Epilepsia* 2011;52(Suppl 1):28–38.
- [75] Richerson GB. Serotonin: The Anti-SuddenDeathAmine?: Serotonin & SUDEP. *Epilepsy Currents* 2013;13:241–4.
- [76] Stockler S, Plecko B, Gospe Jr SM, Coulter-Mackie M, Connolly M, Van Karnebeek C, et al. Pyridoxine dependent epilepsy and antquinotin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. *Mol Genet Metab* 2011;104:48–60.
- [77] van Karnebeek CD, Tiebout SA, Niermeijer J, Poll-The BT, Ghani A, Coughlin II CR, et al. Pyridoxine-dependent epilepsy: an expanding clinical spectrum. *Pediatr Neurol* 2016;59:6–12.
- [78] Coughlin II CR, van Karnebeek CD, Al-Hertani W, Shuen AY, Jaggaumani S, Jack RM, et al. Triple therapy with pyridoxine, arginine supplementation and dietary lysine restriction in pyridoxine-dependent epilepsy: neurodevelopmental outcome. *Mol Genet Metab* 2015;116:35–43.
- [79] Aquilano G, Linnér A, Ygberg S, Stödberg T, Henckel E. Case report: Fatal outcome of pyridoxine-dependent epilepsy presenting as respiratory distress followed by a circulatory collapse. *Front Pediatr* 2022;10:940103.
- [80] Mercimek-Mahmutoglu S, Corderio D, Nagy L, Mutch C, Carter M, Struys E, et al. Lysine-restricted diet and mild cerebral serotonin deficiency in a patient with pyridoxine-dependent epilepsy caused by ALDHT7A1 genetic defect. *Mol Genet Metab Rep* 2014;1:124–8.
- [81] Latzer IT, Pearl PL. Treatable inherited metabolic epilepsies. *Epilepsy Behav* 2024;151:109621.
- [82] Tokatly Latzer I, Pearl PL. Treatment of neurometabolic epilepsies: Overview and recent advances. *Epilepsy Behav* 2023;142:109181.
- [83] van Spronsen FJ, Blau N, Harding C, Burlina A, Longo N, Bosch AM. Phenylketonuria Nat Rev Dis Primers 2021;7:36.
- [84] Koch J, Mayr JA, Alhaddad B, Rauscher C, Biera J, Kovacs-Nagy R, et al. CAD mutations and uridine-responsive epileptic encephalopathy. *Brain* 2017;140:279–86.
- [85] Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, Dyke JP, Cahan H, Slasor P, Jacoby D, Kohlschutter A, Group CLNS. Study of Intraventricular Cerliponase Alfa for CLN2 Disease. *N Engl J Med* 2018;378: 1898–1907.
- [86] Tang M, Park SH, De Vivo DC, Monani UR. Therapeutic strategies for glucose transporter 1 deficiency syndrome. *Ann Clin Transl Neurol* 2019;6:1923–32.
- [87] Wolf B. Biotinidase deficiency:“if you have to have an inherited metabolic disease, this is the one to have”. *Genet Med* 2012;14:565–75.
- [88] Coughlin 2nd CR, Tseng LA, Abdenur JE, Ashmore C, Boemer F, Bok LA, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsies due to α -aminoacidic semialdehyde dehydrogenase deficiency. *J Inher Metab Dis* 2021;44:178–92.
- [89] Tai CH, Lee NC, Chien YH, Byrne BJ, Muramatsu SI, Tseng SH, et al. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. *Mol Ther* 2022;30:509–18.
- [90] Barbour K, Yozawitz EG, McGoldrick PE, Wolf S, Nelson A, Grinspan ZM. Predictors of SUDEP counseling and implications for designing interventions. *Epilepsy Behav* 2021;117:107828.
- [91] Whitney R, Jones KC, Sharma S, RamachandranNair R. SUDEP counseling: Where do we stand? *Epilepsia* 2023;64:1424–31.
- [92] Mesraoua B, Tomson T, Brodie M, Asadi-Pooya AA. Sudden unexpected death in epilepsy (SUDEP): Definition, epidemiology, and significance of education. *Epilepsy Behav* 2022;132:108742.