Epilepsy in Succinic Semialdehyde Dehydrogenase Deficiency, a Disorder of GABA Metabolism

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Abstract

Objectives—Succinic semialdehyde dehydrogenase (SSADH) deficiency is a gamma-aminobutyric acid (GABA) degradative defect. Epilepsy affects half of patients. The murine model is associated with a transition from absence to convulsive seizures in the third week, with fatal status epilepticus.

Methods—The clinical phenotype is reported from a patient database. Flumazenil-Positron Emission Topography (FMZ-PET) and Transcranial Magnetic Stimulation (TMS) were used to study GABA neurotransmission. Electrocorticography, single cell electrophysiology, and radioligand binding studies are reported from animal studies.

Results—Generalized seizures predominate, including tonic-clonic, atypical absence, and myoclonic. EEG discharges are typically generalized spike-wave. MRI shows a dentatopallidoluysian pattern. Sudden Unexpected Death in Epilepsy Patients (SUDEP) has occurred and the associated neuropathology reveals chronic excitotoxic injury in gloubus pallidus. Investigations using FMZ-PET and TMS support downregulation of $GABA_A$ and $GABA_B$ activity, respectively, in patients. Gamma-hydroxybutyrate (GHB) induces spike-wave discharges in homozygous null mice via GHB and $GABA_B$-mediated mechanisms. These resemble absence seizures and are abolished by a $GABA_B$ receptor antagonist. Decreased binding of $GABA_A$ and $GABA_B$ receptor antagonists has been demonstrated in P19 and P14 null mice, respectively.

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Downregulation of GABA$_A$ and GABA$_B$ receptor subunits is observed by P14. GABA$_A$ and GABA$_B$ mediated potentials are reduced from P8–P14.

Conclusion—Generalized epilepsy and epileptiform discharges are characteristic of SSADH deficiency. Spontaneous absence seizures appear in null mice by the third week, which may be induced by GHB or GABA$_B$ activity. Subsequent overuse dependent downregulation of GABA$_A$ and GABA$_B$ receptor activity may be associated with hyperexcitability concomitant with the transition to generalized seizures.

Keywords

SSADH deficiency; epilepsy; absence seizures; generalized convulsive seizures; GABA; GHB

Introduction

SSADH deficiency is an autosomal recessively inherited disorder in GABA degradation that has been reported in approximately 450 people. The enzyme SSADH is involved in the breakdown of GABA to succinic acid via the intermediate succinic semialdehyde, and in its absence, GABA is alternatively converted to GHB (Figure 1). There is a resultant build up of both GABA and GHB in physiological fluids and brain parenchyma. SSADH deficiency is considered likely underdiagnosed due to the heterogeneity in clinical manifestations of the disease, and the high level of clinical suspicion required to test for the disease using specific-ion monitoring for GHB aciduria [1]. Clinical manifestations of the disease include intellectual deficiency, hypotonia, behavioral problems, seizures and ataxia. Most patients present with developmental delay with a mean age of diagnosis of two years, although patients have been diagnosed as late as the third decade. Epilepsy is present in approximately half of affected individuals. Neuroimaging demonstrates increased T2-weighted MRI signal in the globus pallidus (Figure 2), cerebellar dentate nucleus and subthalamic nucleus, along with cerebral and cerebellar atrophy (Figure 3).

The enzymatic deficiency and affected gene locus (Aldh5A1) have been previously identified, and the development of a transgenic mouse model has allowed further study of the physiologic changes produced by SSADH deficiency. The homozygous null mutant animal model expresses a characteristic phenotype with failure-to-thrive, ataxia, and a progressive epileptic disorder characterized by a transition from absence to generalized convulsive seizures and ultimately fatal status epilepticus by the third week of life [2]. The transition from absence to convulsive activity could be analogized to the human epilepsy syndromes of generalized childhood absence or juvenile absence epilepsy as well as juvenile myoclonic epilepsy. The prevalence of seizures in this hyper-GABAergic condition may be viewed as paradoxical. This paper addresses the seizure and EEG data associated with human SSADH deficiency and ongoing research in the human condition and murine model aimed at elucidating the mechanisms underlying epilepsy in this metabolic disorder.

Human Phenotype

Patient Vignette

A 5-year-old boy presented with severe hyperactivity and a new onset generalized convulsion. Neurological examination revealed a minimally verbal, nondysmorphic boy with mild hypotonia, hyporeflexia, and gait ataxia. Psychoeducational testing showed mild intellectual disability (Wechsler Intelligence Scales for Children: verbal 55, performance 65) and deficient adaptive behaviors on the Vineland Adaptive Behavioral Scales. EEG revealed mild background slowing during wakefulness with intermittent generalized spike-wave discharges that were activated during sleep. Valproate was begun but was associated with lethargy. MRI was obtained, demonstrating increased T2-weighted signal in the globus pallidus. Urine organic acids revealed 4-hydroxybutyric aciduria. This led to enzymatic quantification of SSADH enzymatic activity in leucocytes, which confirmed the diagnosis of SSADH deficiency. The patient was treated with lamotrigine with fair seizure control, and has had persistent problems with expressive aphasia, obsessive-compulsive disorder, and anxiety. Now age 25, the patient lives in a group home with other young adults, most of whom have been diagnosed with cerebral palsy, intellectual disabilities, or autism.

Human SSADH deficiency is usually characterized by a relatively nonprogressive encephalopathy manifest in the first two years of life by hypotonia and developmental delay associated with mild ataxia and hyporeflexia. Virtually constant characteristics are intellectual disability and profound expressive language deficits. Psychiatric symptoms tend to be the most disabling and are characterized by inattention and hyperactivity, and sometimes aggression in early childhood, and anxiety and obsessive-compulsive behaviors in adolescence and adulthood [3, 4]. Intermittent decompensation as seen in other metabolic disorders is not the usual presentation, although this is a subgroup (approximately 10% of reported patients) with a more severe phenotype including a degenerative course characterized by regression and prominent extrapyramidal manifestations [5].

A clinical database using systematic questionnaires of 68 patients indicates that developmental delay is a universal presentation. Common clinical features include intellectual disability, behavior problems, and motor dysfunction (Tables 1 and 2). In order to address the long-term outlook, we reported on 33 patients (52% males) over ten years of age [3]. The mean age of this patient cohort is 17.1 years +/− 6.4 years (range 10.1–39.6 years). The mean age when symptoms first appeared was 11 months (range 0–44 months) and the mean age at diagnosis was 6.6 years, although some individuals were not diagnosed until age 25 years.

Nearly half of patients develop epilepsy, usually with generalized tonic-clonic and atypical absence seizures (Table 3) [6]. The epilepsy may be difficult to control, with some patients having sporadic but recurrent episodes of generalized convulsive status epilepticus. We are aware of one patient who died with a diagnosis of SUDEP, and the neuropathology findings are discussed below. Electroencephalographic findings include background slowing, epileptiform abnormalities (usually generalized and sometimes multifocal), and occasionally photosensitivity and electrographic status epilepticus of sleep (Table 4; Figure 4). Heterozygosity for SSADH deficiency has been reported in one family with a parent and

sibling having generalized spike-wave discharges, photosensitivity, and absence and myoclonic seizures [7].

Sleep disorders are common and manifest by excessive daytime somnolence or disorders of initiating and maintaining sleep [6]. We reported sleep study data in ten patients with overnight polysomnograms and diurnal multiple sleep latency studies with prolonged latency to stage REM latency (mean 272 ± 89 min), and reduced stage REM percentage (mean 8.9%,range 0.3% – 13.8%) [8]. Half of patients showed a decrease in daytime mean sleep latency indicating excessive daytime somnolence. Thus, there appears to be a reduction in REM sleep in the disorder. Similarly, animal models have demonstrated that hyperGABAergic states, e.g. via inhibition of GABA transaminase using L-cycloserine, are associated with reduction of REM sleep and prolongation of the transition phase between sleep stages NREM and REM [9].

Radiographic Findings—We have identified a pallidodentatoluysian pattern of increased T2-weighted signal intensity involving the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei bilaterally and symmetrically. Other findings include cerebral atrophy, cerebellar atrophy, delayed myelination, and T2-hyperintensities in subcortical white matter, thalamus, and brainstem [10, 11]. While the pallidal hyperintensity is usually homogeneous and equally affects the internal and external portions, we have had occasional patients with heterogeneous and even asymmetric involvement. Magnetic resonance spectroscopy will show spectra for routine single and multi-voxel studies of N-acetyl aspirate, choline, and lactate, but specialized protocols that allow editing for small molecules has shown elevated levels of GABA and related compounds (including GHB and homocarnosine) in patients but not obligate heterozygotes [12, 13]. Fluorodeoxyglucose PET studies have shown decreased cerebellar glucose metabolism in patients with cerebellar atrophy demonstrated on structural MRI [1, 14].

Neuropathology—Recently the first post-mortem examination of SSADH deficiency became available in the patient diagnosed with SUDEP as noted above. The underlying diagnosis of SSADH deficiency had been made retrospectively in a 19-year old deceased female following the confirmed diagnosis in her living sister. Her living sister had been followed with a history of developmental delay and borderline cognition (IQ = 70), until presenting with seizures and a subsequent diagnosis of SSADH deficiency. The decedent presented with developmental delay, seizure onset at age thirteen years, and death at age nineteen after having experienced escalating convulsive seizure activity. A pathogenic homozygous mutation of Aldh5A1 (p.Gly409Asp) was detected in the living sister, and subsequently confirmed in the decedent. Both parents were confirmed as heterozygote carriers. The major neuropathological finding was striking discoloration of the globus pallidi, which is remarkably consistent with imaging findings in the condition. On microscopic examination, there was hyperemia and granular perivascular calcification of the globus pallidus and superior colliculus, consistent with chronic excitotoxic injury, without significant neuronal loss or gliosis of CA1 of the hippocampus, the area which would have been considered most vulnerable to epileptic or hypoxic injury [15].

Laboratory and Biochemical Findings—Laboratory screening is done with urine organic acids, which consistently show elevated GHB although specific ion monitoring is sometimes necessary to detect an otherwise subtle peak that is close on the spectrograph to the larger and normal urea peak [1]. Specimens also frequently show dicarboxylic aciduria and elevated 3,4-dihydroxyhexanoic acid. Routine laboratory tests as well as plasma amino acids and studies of bioenergetics and mitochondrial screening are noninformative. All physiologic fluids will be elevated in GHB, and in the absence of exogenous administration, confirmation of the enzymatic deficiency should be obtained through either enzymatic quantification, available in leucocytes, or mutational analysis via sequencing of the gene Aldh5A1.

The disorder is associated with characteristic alterations in neurotransmitter concentrations, although CSF neurotransmitter analysis is not required to make the diagnosis. Cerebrospinal fluid has been studied for GABA concentrations and related metabolites [16]. There is a two- to four-fold increase in GABA and 30-fold increase of GHB in CSF [17]. There are also elevated levels of homocarnosine and a trend toward low glutamine levels, implicating dysfunction of the neuronal-glial shuttle wherein glutamine is synthesized only in astroglia with subsequent glutamate and GABA formation in neurons.

Pathophysiology of Epilepsy in SSADH Deficiency—The pathophysiology of absence seizures raises the importance of altered $GABA_A$ and $GABA_B$ mechanisms, which represent fundamental defects in SSADH deficiency. Typical absence seizures usually present as staring episodes associated with three-per-second, generalized spike-wave discharges on EEG. Atypical absence seizures have relatively similar semiology but are associated with a slower spike-wave frequency (1.5–2.5 Hz) and tend to occur in the setting of a symptomatic neurodevelopmental disorder. Absence seizures are caused by alteration of the thalamocortical circuitry involving thalamic relay neurons, thalamic reticular neurons, and cortical pyramidal neurons. Thalamic relay neurons activate cortical pyramidal neurons in either a tonic mode causing wakefulness or REM sleep, or a burst mode that uses T-type calcium channels to produce non-REM sleep. The thalamic reticular neurons hyperpolarize the thalamic relay neurons through $GABA_B$ receptors and cause burst firing during wakefulness, which may lead to absence seizures. The thalamic reticular neurons are in turn inhibited by neighboring reticular neurons through activation of $GABA_B$ receptors. Therefore, both $GABA_A$ and $GABA_B$ receptors are involved in absence epilepsy, with the former mediating the inhibitory post-synaptic potentials regulating thalamocortical behavior and the latter synchronizing thalamocortical circuitry [18].

$GABA_B$ mediated activity is responsible for physiologic de-inactivation of T-type calcium channels that lead to the spike discharge in absence seizures. Hence, excessive $GABA_B$ activity may be predicted to exacerbate absence seizures, as seen with administration of vigabatrin, raising overall GABA levels, or more specifically baclofen, a $GABA_B$ receptor agonist. Further, decreased GABAergic activity could potentially be associated with a transition from absence to generalized convulsive seizures later in life. PET has been performed using the benzodiazepine receptor antagonist FMZ in SSADH deficient patients, unaffected parent heterozygotes and healthy adult controls [19]. Results showed a significant reduction in FMZ binding in the SSADH deficient individuals in comparison to

the controls in all regions of interest: basal ganglia, amygdala, hippocampus, cerebellar vermis, and frontal, parietal and occipital cortices (Figure 5). There was no noted difference in binding between the controls and the heterozygotes. This demonstrates a decrease in the number of $GABA_A$-benzodiazepine binding sites in the central nervous system of patients with SSADH deficiency, and suggests overuse-dependent down-regulation of $GABA_AR$ activity.

Additionally TMS with single and paired-pulse stimuli was performed on eight sets of SSADH deficient individuals and their heterozygous parents [20]. Loss of long interval intracortical inhibition and a reduced cortical silent period were noted in affected individuals when compared to heterozygotes and healthy controls, consistent with diminished $GABA_BR$ cortical activity. Hence, there is evidence of desensitization of both $GABA_A$ and $GABA_B$ receptor activity in vivo, suggesting less GABA mediated inhibition and potentially subsequent predisposition to convulsive seizures.

Murine Model

Absence seizures may be evoked in mice with direct application of GHB [21]. In SSADH deficiency, there is accumulation of both GABA and GHB, as well as dysregulation of multiple amino acids (glutamate, glutamine, alanine, aspartate, serine, taurine, cystathionine, methionine, homocarnosine, arginine) [22]. Of all interventions, NCS-382, a GHB receptor antagonist, has had the highest survival rate in the mutant animal model [1]. Absence seizures may also be artificially induced in the SSADH (−/−) mouse model using baclofen, a $GABA_BR$ agonist, or GHB, which acts via both GHB and $GABA_B$ receptor mediated mechanisms to produce 7Hz spike-wave discharges in thalamocortical circuitry [2]. Absence seizures are abolished in the mouse model with the use of the $GABA_BR$ antagonist CGP35348 [2] or the antiepileptic ethosuximide, which causes voltage dependant blockade of T-type calcium currents. It has also been demonstrated that although the increase in whole-brain GABA contents in SSADH(−/−) mice does not change spontaneous inhibitory postsynaptic currents, a measure of synaptic GABAergic connections, it does increase tonic inhibition in the neocortex through presumed extrasynaptic $GABA_A$ receptors [23]. This implies that the increased extracellular GABA levels may act through extrasynaptic $GABA_A$ receptors to cause excessive cortical GABAergic neurotransmission, thus aiding in absence seizure production in SSADH deficiency.

The transition from absence to generalized convulsive seizures has been demonstrated in the SSADH(−/−) mouse using electrocorticogram (ECoG) recordings in P16 and P20 mice. Compared to an uneventful baseline ECoG of P16 wild type (+/+) mice, P16 SSADH (−/−) mice displayed 250–300μV, 5–7Hz spike-and-wave discharges (SWD) lasting 3–6s in duration (Figure 6. This activity was accompanied by a frozen stare and vibrissal twitching, and was consistent with absence epilepsy. P20 SSADH null mice were also tested using ECoG, and rather than the SWD seen in absence seizures, a generalized 600μV discharge at 5Hz followed by 1.5–2Hz SWD were observed, which was indicative of tonic-clonic seizures. Such generalized tonic-clonic seizures were considered to be the cause of mortality in these SSADH null mice due to the later development of convulsive status epilepticus [2].

The mechanism for induction of absence seizures by GHB in the mouse model does not explain the development of convulsive seizures. A postulate is that absence seizures may evolve into generalized convulsive seizures through overuse-dependent down-regulation of both $GABA_A$ and $GABA_B$ receptors in the presence of high levels of GABA and GHB. This could result in a breakdown of GABA-mediated inhibition, consequently causing cortical hyperexcitability and rendering an epileptogenic state.

Decreased binding of $GABA_A$R antagonist [35S]

Tert-butylbicyclophosphorothionate has been demonstrated in the cortex, hippocampus and thalamus of P19 SSADH(−/−) mice compared to SSADH(+/+) mice before the onset of tonic-clonic seizures [24]. There is specific downregulation of the $GABA_A$R subunit β2 demonstrated through immunohistochemical staining of the SSADH(−/−) mouse brain. Spontaneous rhythmic activity was recorded in 67% of SSADH(−/−) mice, but no spontaneous discharges were seen in the wild type model. Extracellular field recordings in hippocampal CA1 pyramidal layers of P14 SSADH null mice show larger amplitudes of evoked postsynaptic field potentials and an increased number of population spikes. Additionally, a significant reduction in input resistance and resting membrane potential of hippocampal neurons is seen in P14 but not P9 SSADH(−/−) mice. These findings suggest a hyperexcitable state in the pyramidal cells of SSADH deficient mice after the second week of life. $GABA_A$R-mediated IPSPs are also noted to be reduced in hippocampal neurons in both P8 and P14 SSADH null mice. It is hypothesized that this demonstrated decrease in surface $GABA_A$R activity in SSADH deficient mice may be due to increased receptor endocytosis in the presence of increased GABA levels and prolonged occupancy of $GABA_A$ receptors [24].

There is parallel evidence for $GABA_B$ downregulation in the null mouse [9]. Decreased binding of the $GABA_B$R antagonist CGP54626A is seen throughout the brain, and particularly in the hippocampus of both P7 and P14 SSADH(−/−) mice when compared to wild type. Moreover, there is a significant decrease in $GABA_B$ mediated synaptic potentials in both P7 and P14 SSADH(−/−) mice compared to wild type mice. Prolonged agonist treatment of $GABA_B$ receptors appears to result in increased endocytosis of $GABA_B$R with resultant decrease in receptor function, again supporting use-dependent $GABA_B$ downregulation, which may mediate the development of generalized convulsive seizures.

Treatment Strategies and Clinical Trials—Treatment for SSADH deficiency remains problematic and no consistently successful therapy has emerged [25]. Treatment is symptomatic and targeted to clinical deficits. Options include anxiolytic agents or selective serotonin reuptake inhibitors (SSRIs) and related medications for obsessive-compulsive disorder. Appropriate antiepileptics are chosen for generalized epilepsy other than avoidance of valproate due to its ability to inhibit any residual SSADH enzymatic activity [26]. Hence, worsening of the patient in the vignette provided (*vide supra*) was attributed in retrospect to the metabolic diagnosis. Antiepileptics used successfully for maintenance therapy have been lamotrigine, levetiracetam, and topiramate.

Vigabatrin, an irreversible inhibitor of GABA-transaminase, is a logical choice because it will inhibit the conversion of GABA to GHB, a putative pathogen in this condition. A video-manuscript report of two adolescent brothers demonstrates exercise-induced paroxysmal dyskinesias, manifest by a prominently lurching gait, which showed some improvement following vigabatrin therapy [27]. Vigabatrin, however, has not been a consistently helpful therapeutic for these patients, and there have been many reports of lack of effect or, worse, worsening of symptoms ranging from seizure control to alertness. Further, safety concerns persist regarding retinal toxicity of vigabatrin, especially in this patient population that is unable to report visual field defects. In clinical trials, 30% of patients treated with vigabatrin for epilepsy report visual field defects following one year of treatment [28, 29, 30] MRI signal changes caused by vigabatrin, particularly prominent in the GABA-rich thalamus and basal ganglia, pose additional concerns regarding vigabatrin use in SSADH deficiency [8, 9]. While vigabatrin will lead to at least transient decreases in CSF GHB levels [31], there may be a deleterious effect related to attendant increases in CSF (and brain) GABA levels [13].

Clinical trials have been proposed and initiated with several agents. Taurine, an amino acid with several possible neurotropic roles, lengthened survival in the SSADH mutant mouse using either intraperitoneal or oral application [32]. Taurine is associated with an observed safe level in humans at 3 grams/day, and higher dosages have been tested without significant adverse effects. In a single case report available as an abstract, taurine was reported to improve gait, coordination and energy of a 2 ½-year-old boy with SSADH deficiency [33]. The patient was given 4 grams/day (~ 200 mg/kg) over one year. Higher doses were associated with insomnia. At 9 months teachers reported improved behavior, peer interactions, increased level of activity and coordination. At 12 months, the boy's MRI was interpreted as improved. No correlation was found between improved behavior and urine GHB levels. The case was neither controlled or blinded, but a clinical trial is in progress at our center.

Animal work in the SSADH mutant model has suggested benefit from treatment with SGS 742, a $GABA_B$ receptor antagonist. Earlier studies had shown promise with a similar compound, CGP-35348 [32, 34]. SGS 742 improves electrocorticographic epileptiform activity in the mutant mouse model. Phase II human studies in adults with mild cognitive impairment have shown significantly improved attention, reaction time, visual information processing, and working memory as well as a good safety profile [35]. Planned clinical trials of this agent in SSADH deficiency are dependent upon access to the compound.

Conclusions

SSADH deficiency is a rare neurometabolic disorder characterized by developmental delay, hypotonia, cerebellar ataxia, and hyporeflexia in early childhood. Epilepsy affects approximately half of patients, and generalized epileptiform abnormalities are common on EEG. The severity of the epilepsy is variable, although some patients have experienced repeated status epilepticus and SUDEP has been reported. ESES has been documented, and a less common but more severe phenotype includes active myoclonic seizures. In the murine model, early absence seizures transition into generalized convulsive seizures, and ultimately

lethal status epilepticus in the third week of life. Correlation of murine and human data suggest that absence seizures are related to excessive GHB and $GABA_B$ mediated activity, and generalized convulsive seizures may be an effect of overuse dependent down-regulation of $GABA_A$ and $GABA_B$ receptor activity. The latter would result in a hyperexcitable state and thus epileptogenesis in this hyper-GABAergic disorder.

Acknowledgements

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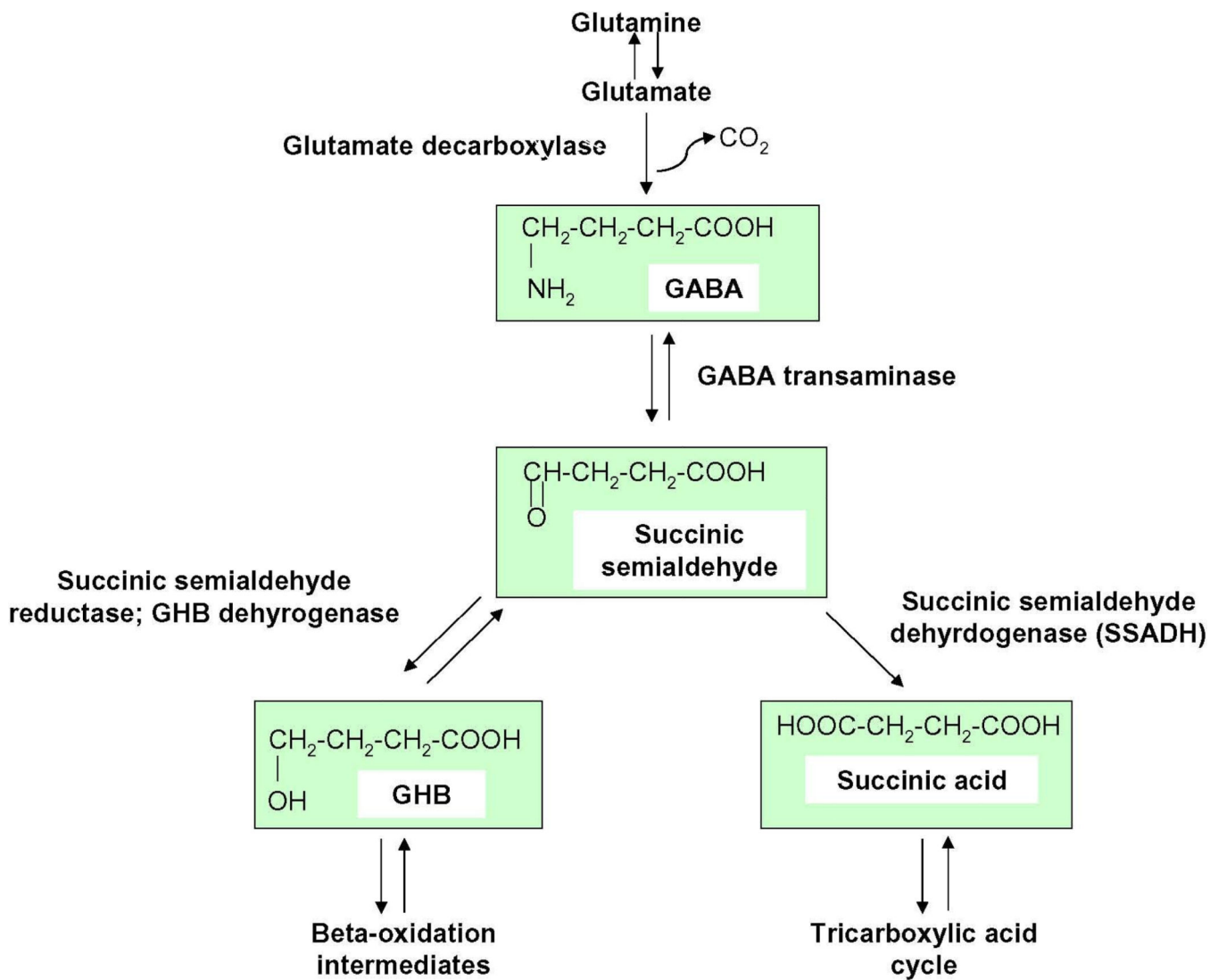
Figure 1. GABA degradation pathway

GABA is normally converted via GABA-transaminase to succinate semialdhyde, which is then broken down to succinic acid by succinate semialdehyde dehydrogenase (SSADH). In the absence of SSADH, succinate semialdehyde is converted to GHB rather than succinic acid, and this leads to a build up of both GHB and GABA in the brain.
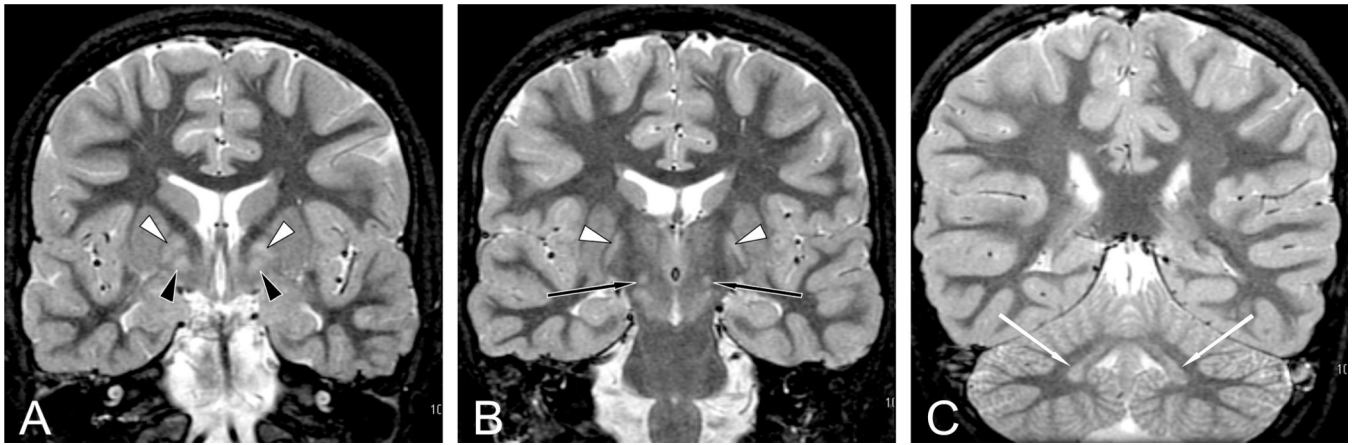
Figure 2. Dentatopallidoluysian Pattern in SSADH Deficiency
Coronal short tau inversion recovery sections from MRI in patient with SSADH deficiency showing bilateral symmetric homogenous signal abnormalities in each globus pallidus pars lateralis (white arrow, A and B), pars medialis (black arrow, A), subthalamic nucleus (black arrows, B), and dentate nucleus (white arrows, C). (Reprinted with permission from Pearl et al: Neurology 2009;73:423–9.)
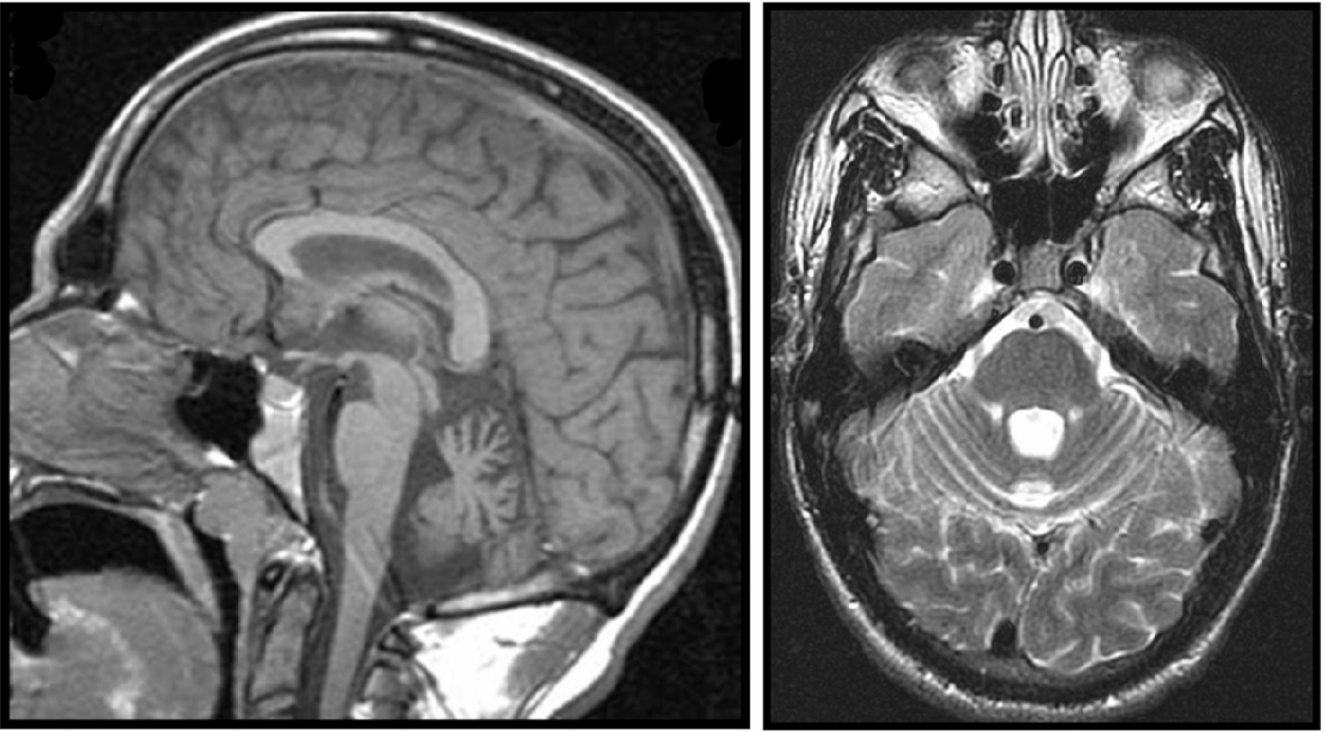
Figure 3. MRI of patient with SSADH deficiency- midsagittal and axial
Midsaggittal (left) and axial (right) 1.5 T MRI demonstrating cerebellar atrophy predominantly affecting the midline vermis. (Reproduced with permission from Acosta et al. J Child Neurol 2010 May 5. [Epub ahead of print].)
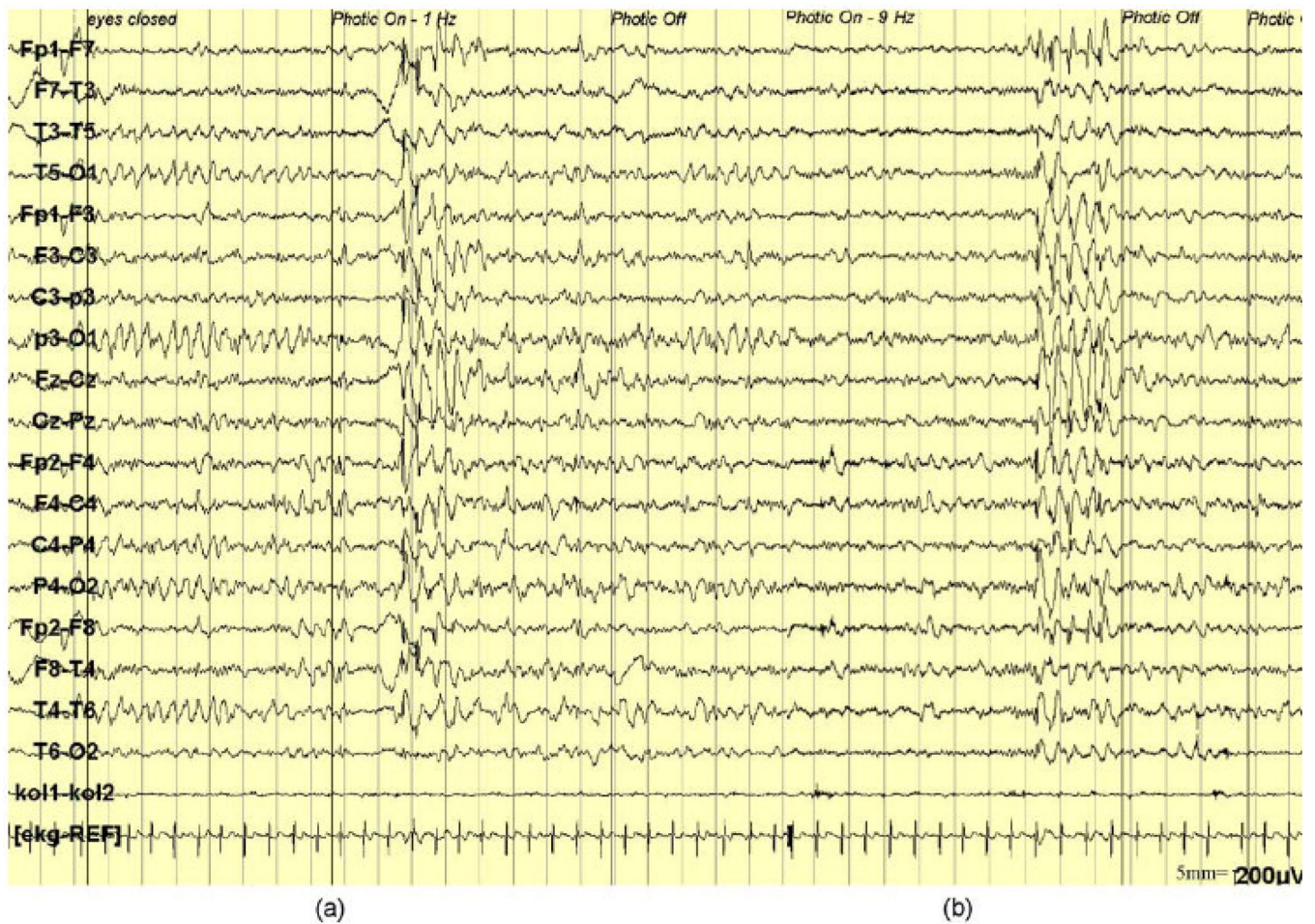
Figure 4. EEG abnormalities in SSADH deficiency
(a) Intermittent photic stimulation (IPS) at 1 Hz causes bilateral 2.5 Hz spike-waves with frontocentral predominance. (b) 9 Hz IPS causes bilateral, diffuse spike-and-wave discharges (Reproduced with permission from: Dervent et al: Clin Neurophysiol 2004;115:1417–22.)
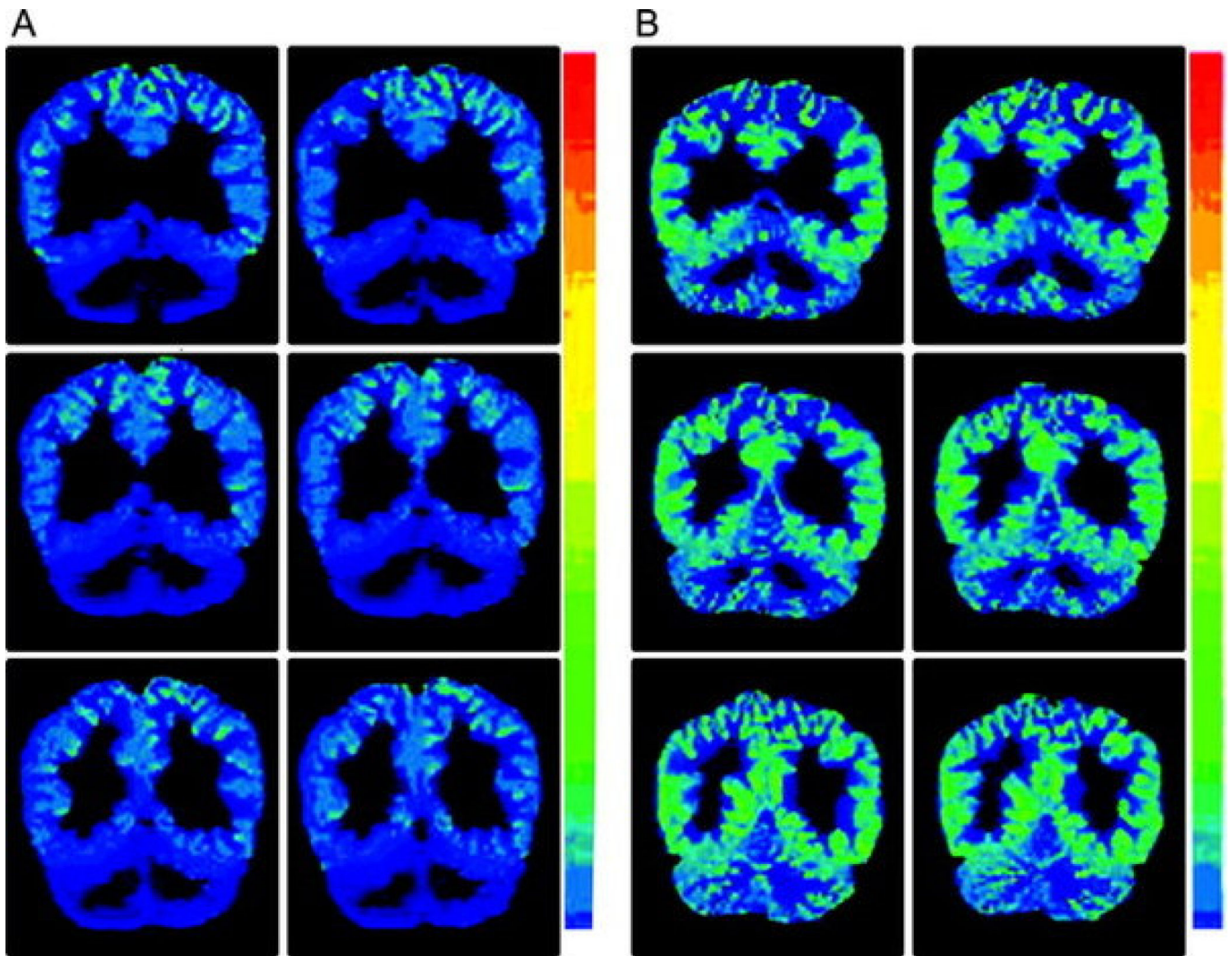
Figure 5. Decreased GABA$_A$ binding on FMZ-PET in SSADH deficiency
FMZ-PET shows marked reduction of cortical binding potential of [11C]-flumazenil in patient with SSADH deficiency (A) versus heterozygote control (B). (Reproduced with permission from Pearl et al. Neurology 2009;73:423–9.)
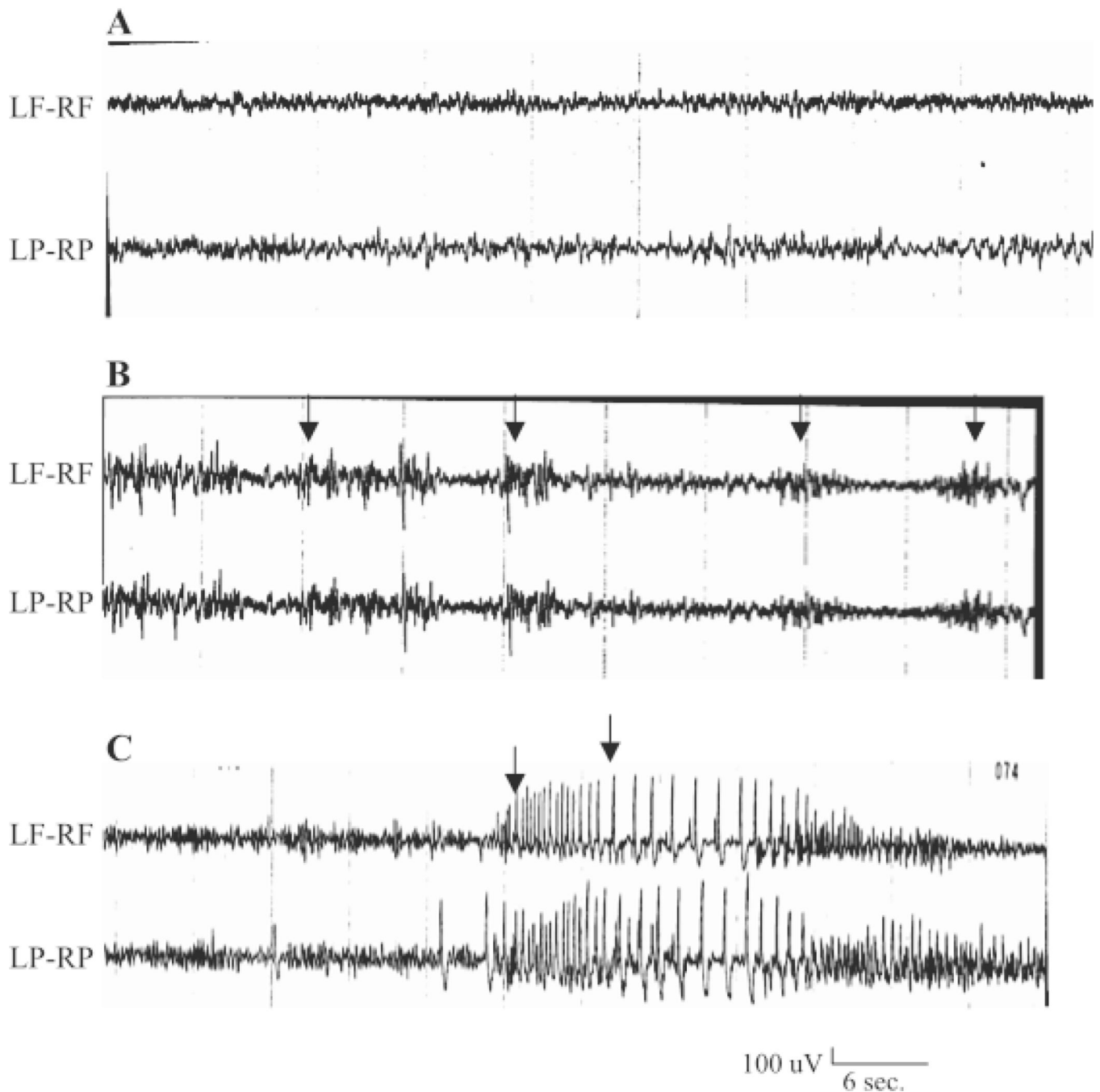
Figure 6. Transition from absence to tonic-clonic seizures in P20 SSADH(−/−) mice
(A) Baseline electrocorticogram (ECoG) recordings in P16 wild-type (+/+) mice show uneventful 35–50 uV and 5–7 Hz oscillations. (B) ECoG of P16 SSADH (−/−) mice reveals 250–300 uV, 5–7 Hz spike-and-wave discharges (SWD) lasting 3–6s duration. This was associated with frozen stare and vibrissal twitching, suggesting absence seizures. (C) ECoG recording in P20 SSADH(−/−) mice show a transition from absence to a generalized 600 uV at 5 Hz followed by 1.5 to 2 Hz SWD associated with tonic-clonic seizures (arrow). LF= left

frontal, RF= right frontal, LP= left parietal, RP= right parietal. (Reproduced with permission from: Cortez et al. Pharmacol Biochem Behav 2004;79:547–53.)

Table 1

Clinical features of SSADH deficiency (n=68)

	Number	Percentage
Developmental delay	67	98.5%
Mental retardation	65	95.6%
Hypotonia	57	83.8%
Behavior problems	47	69.1%
Seizures	34	50.0%
Ataxia	50	73.5%

Table 2

Neuropsychiatric disturbances in patients with SSADH deficiency (n=43)

	Number	Percentage
Aggression	9	20.9%
Anxiety	17	39.5%
Hallucinations	5	11.6%
Hyperactivity	24	55.8%
Inattention	31	72.1%
Obsessive compulsive disorder	16	37.2%
Sleep disturbances	28	65.1%
Pervasive developmental disorders/autism	5	11.6%

Table 3

Seizure activity in patients with SSADH deficiency (n=34)

	Number	Percentage
Generalized tonic-clonic	18	52.9%
Absence	17	50.0%
Myoclonic	8	23.5%
Unspecified	3	8.8%
Other (Anterior temporal lobe epilepsy, atonic partial, febrile)	16	47.1%

Table 4

EEG findings in patients with SSADH deficiency (n=40)

	Number	Percentage
Normal EEG	17	42.5%
Abnormal EEG	23	57.5%
Background abnormal/slowing	12	30.0%
Spike discharges	11	27.5%
Electrographic status epilepticus during slow wave sleep	1	2.5%
Photosensitivity	3	7.5%