Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency
Neurology 2007;68:1320-1321
DOI: 10.1212/01.wnl.0000259537.54082.6d

This information is current as of April 26, 2007

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/68/16/1320

Neurology is the official journal of AAN Enterprises, Inc. A bi-monthly publication, it has been published continuously since 1951. Copyright © 2007 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.
Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency

V. Leuzzi, MD; M.L. Di Sabato, MD; F. Deodato, MD; C. Rizzo, BiolD; S. Boenzi, ChD; C. Carducci, ChD; P. Malaspina, BiolD; C. Liberame, MD; and C. Dionisi-Vici, MD

Succinic semialdehyde dehydrogenase (SSADH; E.C. 1.2.1.24) deficiency (MIM#271980) is a rare defect of the gamma-aminobutyric acid (GABA) catabolic pathway, resulting in 4-hydroxybutyric acid (GHB) accumulation. We report the occurrence of an unusual paroxysmal movement disorder in two affected siblings born of healthy nonconsanguineous Italian parents.

Case 1. This 18-year-old boy presented during childhood with autism, motor stereotypes (trunk swinging), hyperactivity, clumsiness, and hypotonia. Generalized epilepsy manifested at age 7 years, and sleep disorder (compulsive limb movements) manifested at age 10 years. Starting from age 15 years, he had a transient discomfort in the lower limbs while walking. On examination at age 16 years, he presented severe mental retardation, dystonia, motor stereotypes (chaotic gesticulation, trunk swinging), mild dystonic postures of upper limbs, and paroxysmal exercise-induced dystonia (PED). PED emerged after approximately 100 steps as large amplitude abductor movements of the legs, gait freezing, frightful expression, and occasionally, falling (video E-1 on the Neurology Web site at www.neurology.org); he was able to walk again after resting 5 to 6 minutes. Vigabatrin (30 mg/kg/day) selectively, but partially, improved PED (he recovered the ability to walk for approximately 15 minutes) (video E-2), whereas it did not influence epilepsy and the language disorder.

Case 2. This 13-year-old brother of Case 1 had multifocal seizures, psychomotor delay, and hypotonia during the first months of life. Obsessive–compulsive disorder (OCD) was diagnosed when he was 6 years old. A gait abnormality was noticed at age 11 years. On examination at age 12 years, he presented macrosomia (height and weight >97%, head circumference approximately 70%), mammary hyperplasia, extra nipple on the right, hypertelorism, thoracolumbar scoliosis, myopia, striae cutis distans (on trunk and thigh), and hyperchomatic skin spots. He was moderately mentally retarded (Wechsler Intelligence Scale for Children–Revised IQ 48) and showed OCD, hand mannerisms, motor and vocal tics, poor gross-motor skills and clumsy gait, dystonic posture of upper limbs (right > left), and PED, like his brother. He also had sporadic generalized seizures. Under vigabatrin (20 mg/kg/day), gait clumsiness and exercise-induced dystonia disappeared. He remained seizure free for approximately 1 year.

Sertraline (1 mg/kg/day) improved OCD. After 16 months of vigabatrin treatment, clinical condition remained stationary.

Brain MRI performed before and after the beginning of PED (at 10 and 17 years in Case 1; at 2 and 13 years in Case 2), revealed a stable bilateral involvement (T2-weighted signal increase) of pallidum and dentatum. N-Acetylaspartate, choline, creatine/ phosphocreatine, and myo-inositol were all normal on brain magnetic resonance spectroscopy (GABA was not assessed). Metabolic and molecular (ALDH5A1 gene) alterations are summarized in the table. CSF guanidinoacetate (GAA) was normal (Case 2). Cytogenetic analysis disclosed a normal 46 XY karyotype.

Discussion. Ataxia is the most frequent movement disorder in SSADH deficiency. Choreiform movements, dystonia, choreoathetosis, and myoclonus have also been reported. Our cases developed a paroxysmal movement disorder, never reported in patients with SSADH deficiency, which proved to be responsive to vigabatrin. This drug irreversibly inhibits GABA transaminase, leading to an increase of GABA and a concomitant decrease of GHB in CSF and less markedly and consistently in urine and serum. Because CSF GHB and GABA under vigabatrin were not assessed, we cannot attribute the clinical improvement to one or the other of these two pharmacologic effects. The latency of PED appearance in our patients remains to be explained. The fact that pallidum and dentatum involvement was detected long before the appearance of the movement disorder (and remained unchanged during the course of the disease) does not support a causal linkage between neuroimaging and clinical features. Recently, an accumulation of guanidinoacetate methyltransferase (GAA) and GAA has been reported in the brain of SSADH−/− mice, as well as in urine and CSF (GB) of SSADH-deficient patients. However, GAA level was lower than that found in guanidinoacetate methyltransferase–deficient patients, and we confirm that it is normal in CSF.

GHB concentration in biologic fluids, whose increase is the biochemical marker of SSADH deficiency, was not as high as reported in the literature and lower in urine than in plasma and CSF. GHB levels vary markedly intraindividually and interindividually, possibly decline with aging, and are not correlated with residual enzyme activity or severity of symptoms.

The missense alterations on the ALDH5A1 gene cause a markedly reduced enzyme activity in our cases. According to expression studies, c.278G>T (exon 1) and c.526G>A (exon 3) mutations result in less than 5% of residual enzymatic activity. Finally, patients homozygous for the two mutations were severely affected.Re-,E-,9 (References E-8 through E-11 may be found on the Neurology Web site.)

From the Department of Child Neurology and Psychiatry, University “La Sapienza,” Rome, Italy (V.L., M.L.D.S., C.C., C.L.); Bambino Gesù Children’s Hospital, Rome, Italy (F.D., C.R., S.B., C.D.-V.); and Pediatric Neurology

Additional material related to this article can be found on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the April 17 issue to find the title link for this article.

Table Metabolic and molecular alterations

<table>
<thead>
<tr>
<th>Patients</th>
<th>GHB* urine, mmol/mol Cr</th>
<th>GHB* plasma, μmol/L</th>
<th>GHB CSF, μmol/L</th>
<th>Free GABA CSF, nmol/mL</th>
<th>Enzyme activity, nmol min−1 mg protein−1</th>
<th>ALDH5A1 genotype†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.5 ± 7.0 (4.2–21.4)</td>
<td>22.6 ± 17.9 (5–41)</td>
<td></td>
<td></td>
<td>0.15</td>
<td>c.278G&gt;T (p.C93F)</td>
</tr>
<tr>
<td>2</td>
<td>12.5 ± 2.7 (10–16.2)</td>
<td>23.2 ± 5.6 (16.8–27)</td>
<td>190</td>
<td>138</td>
<td>0.05</td>
<td>c.526G&gt;A (p.G176R)</td>
</tr>
<tr>
<td>Pathologic controls†,‡</td>
<td>94–7,600</td>
<td>96–1,500</td>
<td>245–3,100</td>
<td>370 ± 110 *</td>
<td>40–150</td>
<td>2.53 ± 1.17</td>
</tr>
</tbody>
</table>

* 4-Hydroxybutyric acid (GHB) levels were not influenced by vigabatrin treatment.
† The father was a heterozygous carrier of c.526G>A, and the mother was a heterozygous carrier of the c.278G>T mutation.
Cr = creatine; GABA = gamma-aminobutyric acid.

Clinical/Scientific Notes
Palinacousis in temporal lobe intracerebral hemorrhage

Jong S. Kim, MD; Miseon Kwon, PhD, CCC-SLP; and Jin M. Jung, MD

Palinacousis, an auditory illusion in which perceived aural sensations persist or recur after the initial acoustic stimulus has ceased, may be caused by structural lesions involving the temporal lobe. However, the reported lesions were usually extensive, and detailed imaging tests were rarely performed. We report a patient with transient palinacousis following discrete temporal lobe intracerebral hemorrhage (ICH).

Case report. A 67-year-old hypertensive woman suddenly developed language disturbances. On examination the next day, she was alert, and cranial nerves and motor and sensory functions were intact. Her speech was fluent and mixed with frequent paraphasic errors. She showed difficulty in understanding and naming. The Korean version of the Western Aphasia Battery confirmed that she had severe Wernicke-type aphasia (Aphasia Quotient = 27.2/100). Brain MRI showed an acute ICH in the left middle temporal gyrus (figure). Her language disturbances rapidly improved. Three days after the symptom onset, auditory comprehension (0.5/10 to 7.5/10) and repetition (3.1/10 to 6.7/10) considerably improved, but there remained significant naming deficits (0/10 to 3.4/10).

At this time, she first reported that she intermittently heard “pee-pee,” “tog-tog,” or honey-bee sounds. They were hallucinatory and not repetition or altered perception of environmental sounds. Although irregularly heard, they were heard approximately 10 times a day, more clearly when she got hungry. They were reported to be heard from the “inside” of her brain and not on a particular side. In addition, she occasionally heard voices repeatedly when they actually were no longer produced. For example, when the physician-in-charge said, “Your symptoms are much improved,” she heard “much improved” repeatedly afterward. The

Figure. T2-weighted axial (A), T1-weighted coronal (B), and sagittal (C) MRI shows an intracerebral hemorrhage involving the middle temporal gyrus. Arrows in C indicate superior temporal sulcus.
repeated sounds were usually the fragment of the latter part of the sentence. Sometimes, the sounds were heard a few hours after the actual conversation. Initially, she responded to the voice because she thought that somebody nearby actually talked to her. However, she soon realized that this was illusionary. She denied any history of seizures, psychiatric illnesses, or regular ingestion of drugs or alcohol. During the episode of these symptoms, she remained alert, and no abnormal movements were observed. The symptoms did not disturb her sleep. There were no visual illusion or hallucinations, and musical hallucinations were not heard.

The results of pure tone audiometry and brainstem evoked responses were normal. However, on sound discrimination tests, recognition of environmental sounds was significantly reduced (67% accuracy). EEG showed mild slowing in the left temporal area with normalized discharges. The palinacousis and auditory hallucinations lasted for 3 days with gradual diminution in their frequency, when her aphasia also improved. The symptoms did not recur at 3 months of follow-up, when tests for aphasia and sound discrimination showed normal results.

Discussion. The patient's normal audiometry and evoked responses suggest that the peripheral auditory system was intact. Instead, corticofugal processes were impaired as reflected by her difficulty in recognizing environmental sounds. It is noteworthy that the lesion of our patient was confined to the middle temporal gyrus and did not involve the superior temporal gyrus including the Heschl gyrus or Wernicke area (figure). The rapid improvement of sensory aphasia may be related to the fact that the lesion did not directly damage the Wernicke area.

Palinacousis has occasionally been accompanied by seizure disorders, and the patient's symptoms could possibly have been seizure phenomena. However, this is unlikely because no altered consciousness or abnormal movements were observed. Moreover, EEG findings did not reveal ictal discharges. Nevertheless, the symptom may have been an irritative phenomenon. According to a previous experiment, 12 of 40 subjects experienced hearing or seeing events that occurred in the past, upon electrical stimulation of the temporal lobe. Considering the transient nature of palinacousis, rapid improvement of aphasia, and relatively spared auditory and speech cortices in the superior temporal gyrus, it appears that the symptom may be related to a transient compensatory hyperexcitation of surrounding auditory pathways during the recovery phase of ICH. A previous report described development of hyperemia in the area surrounding the ICH, which was considered responsible for the palinopsia in a patient with parietal ICH. Unfortunately, a perfusion study could not be performed in our patient owing to the transient nature of the symptoms.

Alternatively, the symptom may have been a release phenomenon resulting from transient loss of inhibitory fibers to the auditory system. Whatever is the actual explanation, our patient suggests that palinacousis may be related to a temporal lobe lesion that does not severely damage the primary auditory or speech cortices.

From the Department of Neurology, University of Ulsan, Asan Medical Center, Seoul, South Korea.

Supported by a research fund from Korean Ministry of Health and Welfare (03-PJ1-PG1-CH06-0001) and a grant from Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology of Korea (M103KV10010 06E2201 01010).

Disclosure: The authors report no conflicts of interest.

Received October 2, 2006. Accepted in final form January 3, 2007.

Address correspondence and reprint requests to Dr. J.S. Kim, Department of Neurology, Asan Medical Center, Song-Pa, PO Box 145, Seoul 138-600, South Korea; e-mail: jongskim@amc.seoul.kr

Copyright © 2007 by AAN Enterprises, Inc.

References


Alexander disease with hypothermia, microcoria, and psychiatric and endocrine disturbances

Jemeen Sreedharan, MRCP; Christopher E. Shaw, FRCP; Jozef Jarosz, FRCP; and Michael Samuel, FRCP

A recent article on Alexander disease (AxD)1 made note of the clinical and MRI phenotypic variation that is increasingly seen in this rare progressive leukodystrophy, particularly in late-onset and slowly progressive cases. AxD is caused by mutations in the gene encoding glial fibrillary acidic protein (GFAP), resulting in Rosenthal fiber deposition in astrocytes. It is most commonly seen in infants with sporadic mutations, who present with macrocephaly, seizures, and developmental delay. The disease progresses rapidly to death within 10 years. Adult-onset cases are phenotypically different with more brainstem involvement and slower progression and more likely to demonstrate autosomal dominant inheritance.1,3 The following case highlights previously undescribed features of adult-onset AxD.

Case history. A 38-year-old woman was referred with a 2-year history of progressive difficulty reading with oscillopsia, slurring dysarthria, choking, and stumbling. Her early motor and intellectual development were normal, and she achieved a university degree. At age 32 she developed amenorrhea lasting 9 months, having previously had normal periods, and was found to be osteopenic. Endocrine review concluded she had primary ovarian failure. Her periods and hormone levels gradually normalized. Concurrently she was found to have elevated thyroid-stimulating hormone with low normal T4. She was briefly treated with thyroxine, which was stopped as she was clinically euthyroid. Subsequent thyroid profiles were normal. During this time she also experienced episodes of tearfulness, fatigue, and apathy. A psychiatrist diagnosed depression, and she was briefly treated with imipramine. She later experienced episodes of hypothermia as low as 30 °C. These were associated with ataxia, facial twitching, and drowsiness and normally resolved spontaneously. On one occasion, her level of consciousness became so depressed, concurrent with hypothermia, that she required ventilation on the intensive care unit. Extensive imaging and neurophysiologic and biochemical investigation failed to provide a definitive diagnosis. She eventually recovered back to her usual state within weeks.

When first assessed by us, she was clinically stable and systemically well. She had torsional pendular nystagmus (1 to 2 Hz) in all directions of gaze, synchronous with palatal, tongue, and jaw tremor, without ear clicking. She had asymptomatic microcoria with normal acuities and color vision. She had mild exo deviation for near vision with poor convergence and esodevi ation on lateral gaze, with no weakness of abduction. Other positive findings were mild left arm dysmetria, inability to tandem walk, depressed leg reflexes, and a right extensor plantar response.

Full blood count, liver, renal, bone, and thyroid biochemistry were normal. Viral serology was negative as was Whipple PCR. Autoantibodies were negative, including screens for vasculitis, celiac disease, and Hashimoto encephalopathy. Copper, acanthocytes, organic and amino acids, and very long chain fatty acids were all normal. CSF and muscle biopsy were normal. Genetic tests for spinocerebellar ataxias (SCAs 1, 2, 3, 6 and 7), Friedreich's ataxia, and mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; myoclonic epilepsy with ragged red fibers; and neuropathy, ataxia, retinitis pigmentosa) were negative.
Brain MRI (figure) demonstrated marked symmetric medullary and cerebellar dentate nucleus signal change. The brainstem and cervical cord were atrophic. There was no olivary hypertrophy, and the cerebral hemispheres were normal.

Pupillometry confirmed microcoria with dark diameters of only 1.93 mm in the left eye and 1.78 mm in the right eye. Both pupils showed brisk and normal responses to light and a smaller response to accommodation. Response to 10% phenylephrine was normal, confirming presence of the iris dilator muscle. Review of photographs from her childhood to the present demonstrate a progressive decrease in pupillary diameter. Her father was also reported to have microcoria, raising the possibility of autosomal dominant transmission.

Discussion. The presence of progressive ataxia with palatal tremor, coupled with the MRI findings, suggested the diagnosis of AxD. Mutation screening demonstrated a known GFAP missense mutation (208C→T, Arg70Trp). This change occurs in a highly conserved head domain of the protein. It is predicted to disrupt filament assembly and likely to be pathogenic, confirming the diagnosis of AxD. Her asymptomatic mother and sister were neurologically normal on examination and negative for this mutation. Her father declined interview and DNA sampling.

This case is one of the most slowly progressive to our knowledge and demonstrates a number of well characterized features of adult-onset AxD, such as progressive ataxia, oculopalatal tremor, and isolated brainstem abnormalities on MRI. However, we cannot be certain that AxD is responsible for her transitory disturbances of mood, endocrine function, and temperature regulation. Miosis has previously been documented in a neonate and a young adult, and we would argue that the clinical phenotype of adult-onset AxD should be extended to include progressive microcoria.

References
Vigabatrin improves paroxysmal dystonia in succinic semialdehyde dehydrogenase deficiency


Neurology 2007;68;1320-1321
DOI: 10.1212/01.wnl.0000259537.54082.6d

This information is current as of April 26, 2007