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Chorea in a Patient With Cerebral Palsy: Treatment With Levetiracetam

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Abstract: We report on the case of an adult cerebral palsy patient who developed severe chorea coincident with a febrile illness from a nonstreptococcal infection. The chorea improved markedly with the use of levetiracetam (LEV, Keppra). © 2005 Movement Disorder Society

Key words: cerebral palsy; chorea; nonstreptococcal infection; levetiracetam; Keppra

Cerebral palsy (CP) is a syndrome of motor impairment caused by cerebral damage in utero or during the perinatal period.[1,2] Choreoathetosis occurs in 3% to 5% of individuals with CP.[3] Children with CP may infrequently experience acute paroxysmal choreiform episodes from fever, stress, sudden fright, or excitement.[4–7] We report on the case of an adult CP patient with no prior history of chorea as a child who experienced discreet episodes of severe chorea associated with febrile illnesses due to nonstreptococcal infections. The last episode of chorea improved markedly during treatment with levetiracetam (LEV).

Case Report

A 35-year-old, Hispanic woman with a history of CP was admitted to the hospital in 2004 with a 2-day history of fever of 102°F (38.9°C), and involuntary, flowing movements of her trunk, face, and extremities that began within 24 hours of fever onset. The movements were initially mild but became severe by the second day. Attempts to control the movements with dopamine receptor antagonists (quetiapine 100 mg p.o. once a day), benzodiazepines (clonazepam 1 mg PO t.i.d., Valium 5 mg IV t.i.d.) and antihistamines (Vistaril 25 mg p.o. once a day) failed during the first week of hospitalization, and a neurologic consultation was sought.

Past medical history revealed that the patient had experienced fetal distress and hypoxia during a complicated forceps delivery. She was born at 40 weeks gestation after an 8-hour labor, and weighed 8 lbs, 2 oz. She developed generalized tonic–clonic seizures several hours after birth and was treated with phenytoin and phenobarbital. The patient experienced developmental delays during her early life, including walking at age 2 years and speaking at age 3 years. She could not walk unaided and needed help with activities of daily living, such as dressing and eating. There were no further seizures after her first year. Antiepileptic medications were discontinued when she was 14 years old. The remainder of her past medical history was unremarkable except for recurrent urinary tract infections and Achilles tendon surgery bilaterally for contractures resulting from CP-related spasticity. There was no family history of involuntary movements or neurodegenerative disorders.

At age 27, the patient developed a staphylococcus infection of her right lower extremity. Her temperature reached 102°F (38.9°C), and she developed severe, flowing, involuntary movements of her trunk and extremities concurrently with the onset of fever. A general neurologist diagnosed her with chorea, and administered diazepam 5 mg p.o. t.i.d., haloperidol 0.5 mg p.o. b.i.d., and clonazepam 1 mg p.o. t.i.d.. These medications only minimally reduced the chorea during the first 3 weeks. A work-up for rheumatic fever included a normal echocardiogram and negative anti-streptolysin O titer (ASO) titer. Further testing did not reveal evidence of collagen vascular disease. The chorea gradually attenuated and became mild after 3 to 4 weeks but never completely dissipated.

At age 32, the patient developed an abscessed tooth from an unknown organism. She had a fever of 102°F (38.9°C), and her chorea, which was mild at baseline, again became severe with the onset of fever. A general neurologist treated her with divalproex sodium (Depakote) 250 mg p.o. t.i.d., diazepam 5 mg p.o. t.i.d., hydroxyzine (Vistaril) 25 mg p.o. once a day, and clonazepam 1 mg p.o. t.i.d. The medications did not initially reduce the chorea, which gradually became mild within 3 to 4 weeks. The patient experienced mild chorea until the present time.

During the current hospitalization, the patient experienced fevers up to 102°F (38.9°C) and concurrent severe chorea. She was diagnosed with a urinary tract infection from *Enterococcus coli* and an aspiration pneumonia and was treated with levofloxacin (Levaquin) and acetaminophen (Tylenol). Despite the resolution of fever after 4 days, the chorea did not improve and was severe enough to warrant restraints to keep her from falling out of bed. Her medications during the current hospitalization included diazepam 5 mg IV t.i.d., clonazepam 1 mg p.o. t.i.d., hydroxyzine 25 mg p.o. once a day, and quetiapine 100 mg p.o.

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q.h.s., which were used in an attempt to control the chorea. There was no reduction of chorea, despite the use of these medications for 7 days.

The patient was evaluated by a neurologist specializing in movement disorders (T.A.Z.) on the seventh day after fever onset. On physical examination, the patient was nonverbal and nonambulatory but could follow simple commands, similar to her baseline level of function. Blood pressure was 125/78, pulse 98 beats per minute, and respiratory rate 16 per minute. The maximum temperature during the hospital stay was 102°F (101.5°F at the time of examination), with a pulse of 98 beats per minute. There was no heart murmur or rash. Cranial nerves II through XII and motor strength were normal. Deep tendon reflexes were diffusely increased and extensor plantar responses were present bilaterally. The patient exhibited severe, involuntary, nonpatterned, temporally irregular, flowing movements of her trunk and upper and lower extremities that were consistent with chorea.

Serum chemistries were normal, but the white blood cell count was 35,000 cells/mcl with 78% polymorphonuclear cells. The ASO titer, anticardiolipin antibodies, complement C3 C4, antiphospholipid antibodies, lupus anticoagulant, ceruloplasmin, rheumatoid factor, uric acid, antinuclear antibodies, creatine kinase, and thyroid function tests were normal. The erythrocyte sedimentation rate was elevated at 40 mm/hr (normal range, 1 to 20 mm/hr). Blood cultures were negative, but urinalysis demonstrated cloudy urine with many bacteria. A urine culture confirmed greater than 100,000 enterococci, and the patient was treated with levofloxacin (Levaquin) 500 mg p.o. per day for 14 days. Chest X-ray revealed a mild pneumonia, probably from aspiration, but the patient did not experience oxygen desaturation. An electrocardiogram and echocardiogram were normal. Magnetic resonance imaging of the brain demonstrated mild cerebellar atrophy with no evidence of cerebral infarction. The patient's chronic use of phenytoin may have contributed to the cerebellar atrophy. A 21-lead awake electroencephalogram showed mild generalized slowing without epileptiform discharges.

On day 7 of the hospital admission, the patient was treated with levetiracetam (LEV) 1,000 mg PO b.i.d. in an attempt to control the severe chorea. There was marked improvement in chorea 48 hours after starting LEV. The patient was discharged home at day 10 with no signs of a urinary tract infection, resolving pneumonia, and mild chorea. After 2 weeks, the patient's family discontinued the LEV, and moderate chorea recurred within 48 hours. LEV was restarted and titrated up to 1,000 mg b.i.d. The patient's family reports that the patient experiences mild chorea if they forget to give her a dose of LEV but that she demonstrates little to no chorea with LEV. She has continued to take LEV for chorea control for the past 20 weeks.

To quantify improvement, two physicians who were blinded to the purpose of the videotape as well as treatment independently rated videotapes of the patient using the Abnormal Involuntary Movement Scale (AIMS)[8] (see video Segment 1). The first segment was made 7 days after chorea onset; the second segment was made 48 hours after LEV treatment (i.e., 9 days after chorea onset). Neither blinded rater in our case was familiar with the patient's history and treatment.

The AIMS score of the first rater (J.B., a general neurologist) was 22 of 28 before treatment with LEV and 13 of 28 after treatment with LEV. The AIMS score of the second rater (A.E.L., a movement disorder specialist) was 25 of 28 before treatment with LEV and 15 of 28 after treatment with LEV (Table 1).

TABLE 1. *AIMS scores pre- and post-treatment with LEV*

Area	Rater 1		Rater 2	
	Pre-LEV	Post-LEV	Pre-LEV	Post-LEV
Facial and oral movements	3	2	3	2
Lips and perioral area	2	2	3	2
Jaw	1	2	3	2
Upper extremities	4	2	4	2
Lower extremities	4	1	4	2
Truncal movements	4	2	4	3
Severity of abnormal movements	4	2	4	2
Total	22	13	25	15

AIMS, Abnormal Involuntary Movement Scale; LEV, levetiracetam.

Discussion

This report is a case of an adult CP patient who experienced several episodes of severe chorea when she developed febrile illnesses from nonstreptococcal infections. Although the severe chorea responded only minimally to antidopaminergic medications and benzodiazepines, it improved substantially with LEV. AIMS scores improved approximately 40% after initiation of LEV.

There are several reported cases of chorea in CP patients that worsened with the development of nonstreptococcal infections and febrile illnesses.[1–3] Our patient differs from these patients, because she had no chorea before developing the initial staphylococcus infection. However, similar to these cases, she had no past or current evidence of rheumatic fever, Sydenham's chorea, Huntington's disease, Wilson's disease, drug-induced chorea, or autoimmune or collagen vascular disease.

The cause of our patient's chorea exacerbation is unknown. Anand and Thakur described 40 cases of "cryptogenic" or pure chorea in Pondicherry and the adjoining areas of South India in non-CP patients that resulted from nonstreptococcal infections.[9] Sixty percent of patients were between 10 and 15 years old, 20% were over 15 years old, and 20% were below 10 years old. Seventy percent of patients experienced nonspecific fevers that lasted for 2 to 4 days. Chorea was generalized in most of the cases (90%), and subsided in 3 to 4 weeks in 8 patients (45%). Twelve patients (30%) were treated successfully with haloperidol. Although our patient derived little benefit from dopamine antagonists including haloperidol, her chorea greatly improved with use of LEV. Spontaneous remission of chorea in our patient after LEV treatment is unlikely, because her chorea improved abruptly during the second week after fever onset, compared with her previous choreic episodes, in which the chorea gradually diminished during a 3 to 4 week period. After discharge, the patient's chorea worsened when LEV was discontinued, and attenuated when it was re-started.

LEV is an antiepileptic medication that is approved as monotherapy or as an adjunct to treat partial-onset seizures at doses of 1,000 to 3,000 mg/day.[10,11] It is a structural analogue of piracetam, a drug that reduces cortical myoclonus.[12] Preliminary animal studies and case reports indicate that LEV can

improve dystonia,[13] myoclonus,[14] paroxysmal choreoathetosis,[15] and levodopa-induced dyskinesia.[16] Our case report suggests that LEV could play a role in the treatment of chorea from CP and might be evaluated for chorea from other causes (e.g., Huntington's disease). An advantage of LEV over agents such as haloperidol is that it is not known to cause tardive dyskinesia. Further testing of LEV in a case series or a controlled trial of choreiform patients is warranted to further assess its safety and efficacy.

Legend to the Video

A 35-year-old woman with cerebral palsy developed chorea when she experienced a fever from a nonstreptococcal infection. **A:** Video before treatment with levetiracetam (Keppra, LEV) shows the patient with severe chorea. **B:** The patient 48 hours after starting LEV 1,000 mg twice a day. Substantial improvement in chorea is demonstrated.

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Levodopa-Responsive Infantile Parkinsonism Due to a Novel Mutation in the Tyrosine Hydroxylase Gene and Exacerbation by Viral Infections

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Abstract: Autosomal recessive forms of infantile dystonia due to mutations in the tyrosine hydroxylase (*TH*) gene have been described recently. The main clinical manifestations are Segawa's disease, or infantile hypokinetic rigid Parkinsonism. Here, we report on a patient with hyperrigidity, psychomotor developmental delay, and dystonic posturing of the hands, symptoms that appeared after a viral infection at the age of 14 months. Low homovanillic acid/5-hydroxyindolacetic acid (HVA/5HIAA) ratio in cerebrospinal fluid suggested a TH deficiency. Molecular analysis revealed a novel (H246Y) and a known (D498G) compound heterozygote mutation in the *TH* gene. The patient showed a remarkable response to treatment with levodopa. The new mutation and the association of viral infections with the onset and worsening of symptoms are discussed. © 2005 Movement Disorder Society

Key words: autosomal recessive dystonia; infantile dystonia; tyrosine hydroxylase; levodopa; viral infection

In recent years, the genetic basis of several forms of primary dystonias have been elucidated. They may occur as autosomal dominant, autosomal recessive or as X-linked recessive forms, and are inherited as monogenic traits.[1] Mutations in the responsible genes, lead to biochemical defects in the neurotransmitter synthesis of the basal ganglia, whereas neuroanatomical structures are usually preserved.[1]

Dopa-responsive dystonia with childhood-onset dystonia and a dramatic response to levodopa is due to at least two different genetic defects. The most common form is caused by mutations in the GTP-cyclohydrolase I gene, the first enzyme in the biosynthesis of tetrahydrobiopterin (BH4) from GTP. This form is inherited

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