

## LEVODOPA DOSE-LIMITING DYSKINESIAS IN TREATMENT OF SEGAWA DISEASE

Researchers at the University of Cordoba, and other centers in Spain, Germany and New York report an atypical phenotype of persistent, low-dose levodopa treatment-limiting dyskinesias in 2 members of a family (female child aged 13 years and mother) with prominent brachial dystonia and a novel GCH1 mutation. The girl proband developed severe writer's cramp at age 10 years and persistent treatment limiting dyskinesias, despite continuous levodopa therapy from age 7 years. Even low doses of levodopa (1.1-1.4 mg/kg/day) were associated with postural tremor and worsening of dystonia and writer's cramp. An improvement in dystonia followed an increase in the dose of levodopa to 2 mg/kg, but further increases resulted in dyskinesias, characterized by choreic movements and persistence of writer's cramp. The addition of trihexyphenidyl 6 mg/day and continued levodopa at 0.8 mg/kg/day controlled the dyskinesias. Dyskinesias as limiting side effects of levodopa should not preclude a diagnosis of dopa-responsive dystonia and Segawa disease. (Lopez-Laso E, Beyer K, Opladen T, Artuch R, Saunders-Pullman R. Dyskinesia as a limiting factor in the treatment of Segawa disease. *Pediatr Neurol* 2012 June;46:404-406). (Respond: Dr Lopez-Laso, Pediatric Neurology Unit, Department of Pediatrics, University Hospital Reina Sofia, Maimonides Institute of Biomedical Research of Cordoba, University of Cordoba, Av Menendez Pidal s/n, 14004 Cordoba, Spain. E-mail: elolaso@gmail.com).

COMMENT. Segawa disease is distinguished from *idiopathic torsion dystonia* (ITD) or Oppenheim's dystonia, autosomal dominant primarily affecting Ashkenazi Jewish families and presenting at about 10 years of age. ITD begins in the foot or arm and is progressive. *Dopa responsive dystonia* (DRD) or Segawa variant is autosomal dominant due to a mutation in the GCH-1 gene and deficiency of the enzyme guanosine triphosphate cyclohydrolase I. Diagnosis is by CSF analysis for reduced biogenic amines and pterins. DRD presents in early childhood, usually with foot dystonia, worse later in the day and better after sleep (diurnal variation in symptoms). DRD is usually responsive to small doses of levodopa, and levodopa-induced dyskinesias are typically absent. Some patients present with parkinsonism features. *Focal dystonias* (eg. blepharospasm, torticollis, writer's and musician's cramp), the most common forms of dystonia, typically affect women 40–60 years of age, but may also occur in children with dopa responsive dystonia. The pathophysiology of DRD is reviewed by Segawa M et al. *Ann Neurol* 2003;54 Suppl 6:S32-455).

## LEUKOENCEPHALOPATHIES

### MRI AND INFANTILE-ONSET LEUKOENCEPHALOPATHY

Researchers at VU University Medical Center, Amsterdam and other international centers reviewed the MRIs of >3000 patients with an unclassified leukoencephalopathy, and 7 patients (3 male) shared similar MRI abnormalities and clinical and laboratory

findings. Between ages 9 months and 2 years, MRIs showed signal abnormalities of deep cerebral white matter, corpus callosum, thalamus, basal ganglia, brainstem, and cerebellar white matter. A rim of periventricular white matter was preserved. At follow-up, abnormalities gradually improved. Clinical manifestations were correlated with the MRI findings. Clinical regression occurred in the second half-year of life with limb spasticity, axial hypotonia, and loss of milestones and accompanied by elevated blood and CSF lactate levels. After 2 years of age, patients showed clinical improvement and normal lactate. Lysosomal enzyme activities in leukocytes, especially arylsulfatase A and galactocerebrosidase, were normal. Acylcarnitine, amino acid, urinary organic acid, and very-long-chain fatty acid levels were normal. Mitochondrial DNA screening for mutations was negative. The patients represented a single novel leukoencephalopathy, probably caused by a mitochondrial defect. (Steenweg ME, Vanderver A, Ceulemans B, et al. Novel infantile-onset leukoencephalopathy with high lactate level and slow improvement. *Arch Neurol* 2012 June;69(6):718-722). (Respond: Marjo S van der Knaap MDPH, Department of Child Neurology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands (E-mail: ms.vanderknaap@vumc.nl).

COMMENT. Metachromatic leukodystrophy, Krabbe's disease, Alexander disease, adrenoleukodystrophy, and known mitochondrial diseases were excluded.

The first author of the above paper also reports a leukoencephalopathy with thalamus and brainstem involvement and high lactate 'LTBL' caused by EARS2 mutations. (Steenweg ME et al. *Brain* 2012 May;135(Pt5):1387-1394). In a cohort of 12 patients, this mitochondrial encephalopathy was either mild or severe, with infantile onset, rapidly progressive MRI abnormalities and increased lactate. Patients in the mild group partially recovered and regained milestones at follow-up, MRI improved, and lactate levels fell toward normal. Patients in the severe group had persistent neurological regression, brain atrophy on MRI, and increased lactate. MRI was hallmarked by symmetrical cerebral white matter abnormalities sparing the periventricular rim, and symmetrical abnormalities of the thalami, brain stem, and cerebellar white matter.

## INFANTILE-ONSET ALEXANDER DISEASE

Researchers at the All India Institute of Medical Sciences, New Delhi, India, and VU University Medical Center, Amsterdam report a 6-year-old Indian boy with infantile-onset Alexander disease having an unusually mild clinical course and a de novo mutation in the glial fibrillary acidic protein (GFAP) gene. He had a large head and delayed motor milestones since infancy. He sat at 2 years of age and walked at 3 and 1/2 years. Left focal seizures at 3 years of age were controlled by sodium valproate. Neuro exam revealed hypotonia, brisk reflexes, and extensor plantar responses. MRI showed T2 signal changes in cerebral white matter, mainly frontal. Genetic analysis confirmed the diagnosis and his condition had remained stable for 18 months. (Ramesh K, Sharma S, Kumar A, Salomons GS, van der Knaap MS, Gulati S. Infantile-onset Alexander disease: A genetically proven case with mild clinical course in a 6-year-old Indian boy. *J Child Neurol* 2012 May 7 [Epub ahead of print]). (Response: Sheffali Gulati MD. E-mail: sheffaligulati@gmail.com).