

comprehension at age 26, but not at age 53. The effect on reading was not solely driven by late developers. Speech development was related to reading comprehension at age 26 even when late developers were excluded. Later speech developers were less likely to progress beyond basic education. (Murray GK, Jones PB, Kuh D, Richards M. Infant developmental milestones and subsequent cognitive function. *Ann Neurol* August 2007;62:128-136). (Respond: Dr Graham K Murray, Brain Mapping Unit, Department of Psychiatry, University of Cambridge, c/o Experimental Psychology, Downing Street, Cambridge CB2 3EB, UK. E-mail: [gm285@cam.ac.uk](mailto:gm285@cam.ac.uk)).

COMMENT. Later development of motor milestones and speech is associated with a small but significant impairment of intellectual function and educational attainment. The authors postulate a connection between delayed development of cortical-subcortical circuits in infancy and later cognitive dysfunction. A correlation between severe delay in developmental milestones and subsequent learning disability or mental retardation is well documented (von Wendt L et al. *J Ment Defic Res* 1984;28:219-225). In contrast, in the normal population it has been assumed that mild to moderate modifications of motor and speech developmental milestones are not related to later intellectual function. In a recent longitudinal birth cohort study by the Cambridge group of a Finnish population-based sample, it was found that a more rapid infant motor development is linked to better school performance and higher adult IQ scores. (Murray GK et al. *J Child Psychol Psychiatry* 2006;47:25-29). Frontal cortex, basal ganglia, and cerebellum volume is linearly related to the speed of infant motor development, according to one recent report. (Ridler K et al. *Proc Natl Acad Sci USA* 2006;103:15651-15656). The importance of developmental studies in the performance of later educational attainment, indicated by the above reports, is also suggested by earlier but smaller nonepidemiological samples cited by the authors. In one report of a primary care cohort of 213 children, the age of learning to walk (a milestone most frequently remembered by a parent) was significantly associated with IQ at age 3 (Capute AJ et al. *Clin Pediatr* 1985;24:671-675).

## **ATAXIC DISORDERS**

### **PRIMARY EPISODIC ATAXIAS**

The clinical and genetic diagnosis, genotype-phenotype correlations, pathophysiology and treatment of primary episodic ataxia syndromes are reviewed by researchers from Departments of Neurology, UCLA School of Medicine, Los Angeles, CA; National Hospital for Neurology, Queen Square, London, UK; Johns Hopkins University School of Medicine, Baltimore, MD; and University of Rochester School of Medicine, NY, USA. Primary episodic ataxias (EA) are autosomal dominant channelopathies that present with attacks of imbalance and incoordination. Six EA are described, but two (EA1 and EA2) affecting multiple families, with mutations in genes *KCNA1* and *CACNA1A*, account for the majority of identified cases. Type 1 (EA1) is characterized by brief episodes of ataxia (seconds to minutes) and myokymia (or "neuromyotonia"), with onset in early childhood. Ataxia is precipitated by physical and emotional stress, startle or sudden movement. Attacks are associated with dysarthria and coarse tremor. Myokymia may be apparent clinically or only by EMG. Phenotypic variants can be associated with partial seizures, tight tendon Achilles,

postural abnormalities in infancy, peripheral weakness without ataxia, and atypical cases may last 5 to 12 hours. The EA1 locus is mapped to chromosome 12q, and 19 missense mutations in KCNA1 have been reported.

Type 2 (EA2), the most common EA, is characterized by longer episodes of ataxia (hours) with spontaneous nystagmus (usually vertical and downbeat) and mildly progressive baseline ataxia. A gaze-evoked nystagmus is elicited between attacks. Attacks begin in early childhood, and are associated with vertigo, nausea, vomiting, and migraine headaches. They are responsive to acetazolamide. EA2 is allelic with familial hemiplegic migraine type 1 (FHM1). The EA2 locus is mapped to chromosome 19p, similar to that of FHM1. EA 3 – 6 are described in only one or two families, but with distinctive genetic features and mapped to different chromosomes. Two North Carolina kindreds with EA4 had late-onset vestibulocerebellar ataxia, vertigo and interictal nystagmus. Linkage analysis ruled out EA1 and EA2 loci.

Differential diagnosis of EA syndromes includes epilepsy, paroxysmal dyskinesias and migraine. Myokymia, an irregular undulation of the surface of muscles, distinguishes cases of EA1, and baseline nystagmus, ataxia and headaches are typical of EA2. Genetic testing is available for EA1 and EA2. In treatment, carbamazepine, valproic acid and acetazolamide are effective for EA1, and acetazolamide, flunarazine and 4-aminopyridine in EA2. (Jen JC, Graves TD, Hess EJ et al. Primary episodic ataxias: diagnosis, pathogenesis and treatment. **Brain** October 2007;130:2484-2493). (Respond: Joanna C Jen, UCLA Neurology, 710 Westwood Plaza, Los Angeles, CA 90095).

**C OMMENT.** Episodic ataxias are characterized by attacks of incoordination and imbalance, with onset in early childhood, and associated with myokymia, nystagmus and sometimes migraine headache or seizures. Attacks may be controlled by acetazolamide and/or carbamazepine. EAs are inherited as autosomal dominant channelopathies with mutations commonly in two genes.

## **METABOLIC DISORDERS**

### **PHENOTYPE OF MITOCHONDRIAL DNA 3243A>G MUTATION**

The prevalence and common clinical manifestations of the mitochondrial DNA 3243A>G mutation in children in a defined population in Finland were studied at the Universities of Oulu and Turku and other centers. Three probands were detected with encephalopathy, diabetes mellitus, or sensorineural hearing impairment, and 27 children as potential mutation carriers, with a prevalence of 18.4 in 100,000. Clinical features in 24 children in 5 families with 3243A>G mutation included migraine and learning disabilities, short stature, sensorineural hearing loss, exercise intolerance, delayed motor and speech development, and progressive encephalopathy. The prevalence was relatively high in the pediatric population, but morbidity in children is low. (Uusimaa J, Moilanen JS, Vainionpää L, et al. Prevalence, segregation, and phenotype of the mitochondrial DNA 3243A>G mutation in children. **Ann Neurol** Sept 2007;62:278-287). (Respond: Dr Majamaa, Department of Neurology, University of Turku, FIN-20014 Turku, Finland. E-mail: [kari.majamaa@utu.fi](mailto:kari.majamaa@utu.fi)).