

## HEREDODEGENERATIVE DISORDERS AUTOSOMAL RECESSIVE CEREBELLAR ATAXIAS

### LONG-TERM FOLLOW-UP OF FRIEDREICH ATAXIA PATIENTS

The results of a long-term prospective follow-up of 104 Friedreich ataxia patients are reported from the Salpêtrière Hospital, Paris, and other centers in France. Patients were examined every 6 months for a median period of 5 years (range, 6 months to 7 years). Eighty-eight were treated with the antioxidant, idebenone and 16 declined. The neurologic status, evaluated using the International Cooperative Ataxia Rating Scale (ICARS) and a quantitative writing test, showed worsening even in patients treated with idebenone and especially in those with onset before age 15 years. The ataxia posture subscore increased faster in ambulant patients with shorter disease durations at baseline. In patients with long disease durations, the ICARS scores reached a plateau, and neurologic progression was underestimated. Oculomotor function evaluated by electro-oculography deteriorated slightly, and cardiac function evaluated by echocardiography, electrocardiography, and Holter monitor showed cardiac hypertrophy at baseline and significant decreases in left ventricular mass and ejection fraction at follow-up. Patients with severe neurologic impairment at baseline also had severe cardiac hypertrophy. Although cardiac hypertrophy decreased with treatment, cardiac function showed no improvement. (Ribai P, Pousset F, Tanguy M-L et al. Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. *Arch Neurol* April 2007;64:558-564). (Respond: Alexandra Durr MD, PhD, Institut National de la Sante et de la Recherche Medicale U679, Hopital de la Salpêtriere, Bd de l'hôpital 47, 75013 Paris, France).

COMMENT. All patients in this study had typical Friedreich ataxia (FA) with confirmed molecular diagnosis mapped to chromosome 9q13. FA is an autosomal recessive disease with onset between 5 and 25 years of age. The prevalence is estimated at 1/30,000 to 1/50,000 in most populations. Clinical manifestations include progressive limb and truncal ataxia, dysarthria, absent reflexes, Babinski signs, and impaired vibration and proprioceptive sense. Asymptomatic cardiac disease with left ventricular hypertrophy is present in 66% of patients, and nystagmus or fixation instability occur in 25%. FA with retained reflexes (FARR), a variant phenotype of FS, is reported in some families (Palau F et al. *Ann Neurol* 1995;37:359-362). The ICARS, with a possible maximum score of 100 and 4 subscores (posture, kinetic function, speech, and oculomotor dysfunction) that increase with severity, has interrater reliability but is not appropriate to evaluate progression of FA in patients with long disease duration.

### CLINICAL PHENOTYPES OF AUTOSOMAL RECESSIVE ATAXIAS

An overview of the most common autosomal recessive cerebellar ataxias is presented by researchers at the UCLA Ataxia Center, Los Angeles. *Friedreich's ataxia-like syndromes* include FA (involving mitochondrial iron metabolism), ataxia with vitamin-E deficiency (vitamin E homeostasis), abetalipoproteinemia (lipoprotein metabolism), and Refsum's disease (peroxisomal disease). *FA-like with cerebellar atrophy syndromes*: late-onset Tay-

Sachs disease (a G-gangliosidosis with deficiency of B-hexosaminidase A), cerebrotendinous xanthomatosis (deficiency of mitochondrial enzyme sterol 27-hydroxylase involved with bile-acid synthesis), DNA polymerase  $\beta$  disorder (mitochondrial recessive ataxia syndrome), and spinocerebellar ataxia with axonal neuropathy. *Early-onset ataxia with cerebellar atrophy*: ataxia telangiectasia; ataxia with oculomotor apraxia types 1 and 2, caused by mutations of the aprataxin and senataxin genes; ataxia of Charlevoix-Sauquenay (sacsin gene); infantile-onset spinocerebellar ataxia (a gene encoding the proteins twinkle and twink); Cayman ataxia (gene encoding caytaxin); and Marinesco-Sjogren syndrome (rare infantile- or childhood-onset ataxia, with cataracts, mental retardation, myopathy, hypogonadotropic hypogonadism, and skeletal deformities). Friedreich ataxia is the most prevalent, and directed genetic testing is recommended based on clinical phenotype, which avoids the expense of an unfocused molecular diagnostic battery. (Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurol* March 2007;6:245-257). (Respond: Dr Susan Perlman, UCLA Ataxia Center, University of California at Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095).

COMMENT. Hereditary ataxias are autosomal dominant, autosomal recessive, X-linked, and mitochondrial. The clinical phenotype is important in the differentiation of these ataxias, especially when a characteristic family history is unavailable. Neuroimaging is also useful to differentiate ataxias with and without cerebellar atrophy.

**Cerebellar ataxia in Norway.** Among 60 individuals from 39 families with ataxia, age at onset was lower for patients with autosomal recessive (ARCA) compared with autosomal dominant cerebellar ataxias (ADCA). Disease prevalence in Oslo is estimated at 2.2/100,000 for ARCA and 3.0/100,000 for ADCA. Surprisingly, no Norwegian family with Friedreich ataxia was found in the patients referred to a Department of Neurology in Oslo. Pediatric patients may have been treated elsewhere. ((Koht J, Tallaksen CME. *Acta Neurol Scand* May 2007;115(Suppl 187):76-79).

## BETAMETHASONE TREATMENT OF ATAXIA-TELANGIECTASIA

The response to corticosteroid therapy in a 3-year-old boy with ataxia-telangiectasia is reported from University of Siena, Italy. The diagnosis was confirmed by molecular testing. Improvements in neurologic signs were noted by the parents when betamethasone was used occasionally to treat asthmatic bronchitis. After 2 or 3 days continuous therapy with betamethasone, 0.1 mg/kg/24 hrs, divided every 12 hours, a beneficial effect was observed. The improvement in stance, gait, and skilled movements was dramatic after 2 weeks of treatment, but adverse effects including increased appetite and body weight and moon face occurred by 4 weeks. Methylprednisolone, 2 mg/kg/24 hrs, divided every 12 hrs, substituted at 4 weeks, was ineffective, and was discontinued. At 6 months follow-up, without therapy, the child showed severe signs of CNS impairment. (Buoni S, Zannoli R, Sorrentino L, Fois A. Betamethasone and improvement of neurological symptoms in ataxia-telangiectasia. *Arch Neurol* 2006;63:1479-1482). (Respond: Raffaella Zannoli MD, Department of Pediatrics, Policlinico Le Scotte, University of Siena, Siena, Italy).