

phenotype may be defined by its association with other autoimmune diseases; 26% index MS cases reported coexisting Hashimoto thyroiditis in 10%, psoriasis (6%), and rheumatoid arthritis (2%). (Barcellos LF et al. **Lancet Neurol** Nov 2006;5:924-931).

The differentiation of ADEM and MS is difficult, and in the above report, a viral prodrome and polysymptomatic presentation, characteristic of ADEM, were common in MS. Dale RC et al (**Arch Dis Child** 2005;90:636-639; **Ped Neur Briefs** June 2005;19:47-48) found that the disseminated demyelinating lesions on MRI are cortical and in deep grey matter in ADEM and periventricular/callosal in location in MS. In another study (Mikaeloff et al. **Brain** 2004;127:1942-1947) the risk of MS is significantly higher with MRI callosal lesions, while basal ganglia lesions are equally frequent in ADEM and MS. The risk of relapse, and subsequent diagnosis of MS in patients initially considered ADEM is 10% in one previous study (Tenenbaum et al. 2002; **Ped Neur Briefs** 2002;16:81).

METABOLIC NEURODEGENERATIVE DISORDERS

DIAGNOSIS AND TREATMENT OF SEPIAPTERIN REDUCTASE DEFICIENCY

The diagnosis and long-term effects of treatment of two cases of sepiapterin reductase deficiency (SRD) are reported from Service de Neuropédiatrie, CHU Montpellier, France; University de Sherbrooke, Quebec, Canada; and centers in Germany and Switzerland. Patient 1, a male with first-cousin Turkish parents, presented with a prolonged afebrile seizure at 6 months of age. Progressive global delay, intermittent dystonic movements, and oculoogyric crises followed. EEG, MRI, and routine metabolic tests were normal. At 18 months he had developed generalized spasticity, and by 7 years of age, symptoms showed a diurnal variation, with ability to walk in the mornings and requiring a wheelchair by afternoon. Patient 2, a female born of nonconsanguineous Caucasian parents, presented with delayed psychomotor signs at 5 months, generalized hypotonia, and oculoogyric crises. At one year dystonic movements and swallowing difficulties developed. She walked at 3 years, hypotonia was replaced by spasticity, and her IQ was measured at 46. Oculoogyric crises stopped at 10 years, the head circumference remained at the 50th percentile, and EEG and MRI were normal. A diagnosis of cerebral palsy was suspected until a CSF neurotransmitter study at 13 years of age confirmed a SRD encephalopathy. CSF sepiapterin levels were elevated, and a phenylalanine loading test showed a marked increase in phenylalanine. Plasma serotonin levels were decreased and plasma prolactin was increased. Sepiapterin reductase activity was deficient in fibroblasts from both patients, a homozygous mutation in the SPR gene was found in patient 1, and a homozygous nonsense mutation in patient 2. Treatment was started at 7 and 12 years of age, initially with levodopa and later, with the addition of 5-hydroxytryptophan. Response was dramatic, with resolution of pyramidal signs, dystonic gait, and tremor, muscle tone becoming normal within 2 years. After 5 year follow-up, patients were in school, language and motor development were improved, mild dystonia persisted, and IQ remained subnormal. CSF sepiapterin and 5-OH-tryptophan and plasma prolactin levels, used to monitor progress, had not completely normalized. (Echenne B, Roubertie A, Assmann B et al. Sepiapterin reductase deficiency: Clinical presentation and evaluation of long-term therapy. **Pediatr Neurol** November 2006;35:308-313). (Respond: Dr

Ehene, Service de neuropediatrie, Departement de pediatrie, Universite de Sherbrooke, 3001, 12e Avenue Nord, CHUS, Fleurimont, Quebec, J1H 5N4, Canada).

COMMENT. Sepiapterin reductase deficiency, an autosomal recessive, dopa-responsive, neurotransmitter disease, presents as an infantile encephalopathy between 2 and 6 months of age with delayed developmental milestones, hypotonia, later replaced by spasticity, oculogyric crises, and dystonic movements, with diurnal variation of motor abnormalities. Diagnosis, often mislabeled as cerebral palsy, is confirmed by CSF examination of neurotransmitters. Treatment consists of levodopa, carbidopa and 5-OH tryptophan. Response is dramatic with improvement in motor function and control of oculogyric crises, but persistence of moderately impaired cognitive function and learning. Neville BGR and colleagues at Great Ormond Street Hospital, London, previously reported 7 cases of SRD from Malta, with similar findings and response to therapy (*Brain* 2005;128:2291-2296; *Ped Neur Briefs* Oct 2005;19:78). The clinical manifestations of SRD resemble the autosomal dominant dopa responsive, Segawa disease (*Ann Neurol* 2003;54(Suppl 6):S32-S45). Infants with unexplained cerebral palsy should be screened for SRD, and patients with action dystonia and/or oculogyric crises should receive a trial of L-dopa.

JUVENILE GM2 GANGLIOSIDOSES

Clinical features and genetic correlations of 21 new case histories and 134 published case reports of juvenile or subacute GM2 gangliosidosis were analyzed to delineate the natural history of the disorder, in a study at the Hospital for Sick Children, Toronto, Canada, and University of Sao Paulo, Brazil. Fifteen of the 21 patients had the Tay-Sachs variant and 6 the Sandhoff variant. The mean age of onset of symptoms was 5.3 +/- 4.1 years, and the mean follow-up was 8.4 years. Presenting symptoms were gait disturbance in 67%, incoordination (52%), speech problems (27%), and developmental delay (29%). Patients became wheelchair-bound after 6.2 +/- 5.5 years. Late signs included muscle wasting at 10.6 +/- 7.4 years, proximal weakness (11.1 +/- 7.7 years), and incontinence (14.6 +/- 9.7 years). Psychiatric disorders and neuropathy were more typical of the Sandhoff variant, and dysphagia, sphincter incontinence, and sleep problems presented earlier in the Tay-Sachs variant. MRI showed cerebellar atrophy in 53%. Symptoms in the 21 new cases were similar to the 134 previous reports. Median survival of the total group of 155 patients was 14.5 years. Presence of R178H and R499H mutations was predictive of early onset and rapid progressive course. G269S or W474C mutations correlated with a later onset and slower progression. HEXA genotype in Tay-Sachs variant cases significantly correlated with clinical course. In both variants, speech deteriorated more rapidly than gait abnormalities. (Maegawa GHB, Stockley T, Tropak M et al. The natural history of juvenile or subacute GM2 gangliosidosis: 21 new cases and literature review of 134 previously reported. *Pediatrics* November 2006;118:1550-1562). (Respond: Joe TR Clarke MD PhD, Division of Clinical and Metabolic Genetics, Hospital for Sick Children, 555 University Ave, Toronto, Ont, Canada M5G 1X8).

COMMENT. Juvenile GM2 gangliosidosis is heterogeneous in age of onset, clinical features, and course. The earlier the onset, the more rapid the progression.