

### Multiple Sclerosis: Should MR Criteria for Dissemination in Time be Less Stringent

Chris H. Polman, MD,<sup>1</sup> Jerry S. Wolinsky, MD,<sup>2</sup> and Stephen C. Reingold, PhD<sup>3</sup>

The International Panel on Diagnosis of Multiple Sclerosis is pleased to see that many research groups have taken steps to validate and refine the recommended "McDonald criteria" for diagnosis of MS.<sup>1</sup> Among those, Dalton and colleagues<sup>2</sup> have suggested an addition to the Panel's recommendation for imaging to determine "dissemination in time" when the initial presentation is a monosymptomatic, clinically isolated syndrome consistent with demyelinating disease and a first image is done within 3 months of presentation. From a retrospective analysis of 56 patients in whom optic neuritis was the most common presentation, the appearance of a new T2-weighted lesion at a 3-month follow-up scan is more sensitive and just as specific for predicting a clinical diagnosis of multiple sclerosis as a new gadolinium-enhancing lesion (the recommended criterion.) The authors suggest expanding the International Panel magnetic resonance imaging criteria to include T2 lesions at the 3-month follow-up in these patients.

The International Panel originally considered, but rejected, the inclusion of new T2 lesions at a 3-month imaging follow-up. The point of this criterion was to identify lesions that clearly represent new pathology. T2 lesions, as Dalton and colleagues note, can arise at any time and thus do not necessarily represent new disease activity since presentation.

At this moment, the generalizability of these new results is not clear. The Queen Square MS Research Center is among the world's most experienced at comparing scans from different time points, using highly standardized protocols with a minimum of repositioning error. They have great expertise, which may not be in place at all centers, at defining what is, and what is not, a *new* T2 lesion. Their baseline scans were performed a median of 5 (range, 1–12) weeks after onset of visual symptoms. This delay will vary in different practices and countries and has considerable bearing on whether an increase in T2 lesion load at 3 months reflects lesions that developed around the time of initial symptoms or truly occurred separated in time from the clinical finding. This problem may be greater still for initial isolated clinical presentations other than optic neuritis.

Despite the demonstrated sensitivity and specificity of including T2 lesions at a 3-month follow-up scan at Queen Square, for most diagnosticians gadolinium-enhancing lesions at that point likely still provide the most unequivocal demonstration of new pathology.

The "McDonald criteria" were intended to be revised as additional data became available. We are grateful for the contribution of Dalton and colleagues and look forward to guidance to ensure that, if incorporated, their suggestion can enhance multiple sclerosis diagnosis in everyday clinical practice.

<sup>1</sup>VU Medical Centre, Amsterdam, The Netherlands;

<sup>2</sup>University of Texas Health Sciences Center, Houston, TX;

and <sup>3</sup>National Multiple Sclerosis Society, New York, NY

### References

1. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50:121–127.
2. Dalton CM, Brex PA, Miszkier KA, et al. New T2 lesions enable an earlier diagnosis of multiple sclerosis in clinically isolated syndromes. *Ann Neurol* 2003;53:673–676.

DOI: 10.1002/ana.10856

### More Transgenic Mouse Models of Dopamine Deficiency

Beat Thöny, PhD,<sup>1</sup> and Nenad Blau, PhD<sup>1</sup>

Recently, Chen and Zhuang<sup>1</sup> reviewed genetic mutations and variations of transgenic mouse models affecting dopamine functions. In their overview, they discussed that transgenic mouse models with genes involved in dopamine synthesis, release, clearance, and receptor signaling present with variable phenotypes. Furthermore, they stressed that the only available mouse model for tetrahydrobiopterin (BH<sub>4</sub>) deficiency is the "*hph-1* mouse," which is not a good model for dopamine deficiency. It was generated by chemical mutagenesis and is still undefined regarding the genetic alterations. These mice present with low GTP cyclohydrolase I activity in the first weeks of life, no significant behavior abnormality, and with transient neurochemical deficiency.<sup>2</sup> Chen and Zhuang emphasized the necessity for a more defined transgenic mouse for GTP cyclohydrolase I (or BH<sub>4</sub> deficiency) as a model for L-dopa-responsive dystonia and other dopamine deficiencies.

We and others described independently a knockout mouse model for neurotransmitter deficiency generated by targeting the 6-pyruvoyl-tetrahydropterin synthase (*Pts*) gene.<sup>3,4</sup> The 6-pyruvoyl-tetrahydropterin synthase is catalyzing the second step in the de novo BH<sub>4</sub> biosynthesis.<sup>5</sup> These mice die perinatally with hyperphenylalaninemia and deficiency of BH<sub>4</sub>, dopamine, and serotonin (Table). The *Pts* mutant mice can be rescued only if treated with BH<sub>4</sub> and the neurotransmitter precursors L-dopa and 5-hydroxytryptophan. Treated mice present with severe dwarfism and low levels of insulin-like growth factor-1 (IGF-1).<sup>3</sup> Treatment resulted in normal blood phenylalanine and almost normal brain serotonin and BH<sub>4</sub> levels, but brain dopamine was still 3% of age-matched controls. Similar to human patients,<sup>5</sup> the *Pts* knockout mouse also presented with hypotonia, hypersalivation, and temperature instability. Obviously, catecholaminergic, serotonergic, and nitric oxide systems are affected differently by BH<sub>4</sub> depletion.<sup>4</sup> Despite lethality during the first days of life, which is not typical for BH<sub>4</sub> deficiency due to mutations in the *PTS* gene in humans, we think that the complete *Pts* knockout mouse is a suitable animal model to study the pathophysiology of BH<sub>4</sub> and monoamine neurotransmitter deficiencies. Also, it is another transgenic mouse model of dopamine deficiency.

Table. Levels of Neurotransmitters and Their Metabolites in Mouse Brain

Genotype	Age (days)	DA (pmol/mg)	HVA (pmol/mg)	5-HT (pmol/mg)	5HIAA (pmol/mg)
<i>Pts</i> <sup>-/-</sup>	1	<0.2	0.6–1.0	0.2–0.4	2.9–3.0
Wild type	35	13.0–24.7	21.7–25.9	6.3–6.6	66.2–95.0

DA = dopamine; HVA = homovanillic acid; 5-HT = 5-hydroxytryptamin; 5HIAA = 5-hydroxyindoleacetic acid.

<sup>1</sup>Division of Clinical Chemistry and Biochemistry, University Children's Hospital, Zurich, Switzerland

### References

- Chen L, Zhuang X. Transgenic mouse models of dopamine deficiency. *Ann Neurol* 2003;54:S91–S102.
- Hyland K, Gunasekera RS, Engle T, Arnold LA. Tetrahydrobiopterin and biogenic amine metabolism in the *hph-1* mouse. *J Neurochem* 1996;67:752–759.
- Elzaouk L, Leimbacher W, Turri M, et al. Dwarfism and low IGF-1 due to dopamine depletion in *Pts*<sup>-/-</sup> mice rescued by feeding neurotransmitter precursors and H4-biopterin. *J Biol Chem* 2003;278:28303–28311.
- Sumi-Ichinose C, Urano F, Kuroda R, et al. Catecholamines and serotonin are differently regulated by tetrahydrobiopterin. A study from 6-pyruvoyltetrahydropterin synthase knockout mice. *J Biol Chem* 2001;276:41150–41160.
- Blau N, Thöny B, Cotton RGH, Hyland K. Disorders of tetrahydrobiopterin and related biogenic amines. In: Scriver CR, Beaudet AL, Sly WS, et al., eds. *The metabolic and molecular bases of inherited disease*. 8th ed. New York: McGraw-Hill, 2001:1725–1776.

DOI: 10.1002/ana.10847

### Disease Penetrance in Amyotrophic Lateral Sclerosis Associated with Mutations in the *SOD1* Gene

Peter M. Andersen, MD, DMSc,<sup>1</sup>  
 Gabriella Restagno, PhD,<sup>2</sup> Heather G. Stewart, PhD,<sup>1,3</sup>  
 and Adriano Chiò, MD, PhD<sup>4</sup>

We welcome the publication by Mayeux and colleagues reporting a novel mutation N19S in the *SOD1* gene in an apparently sporadic case of ALS (SALS).<sup>1</sup> We have recently published a clinical study of 16 novel American *SOD1* mutations,<sup>2</sup> bringing the total number of *SOD1* mutations worldwide to 109. Five modes of inheritance were identified in ALS associated with *SOD1* mutations: (1) dominant inheritance with complete penetrance, (2) dominant inheritance with reduced penetrance, (3) recessive inheritance, (4) recessive inheritance with compound heterozygosity, and (5) de novo mutation.

The first group is easily identified clinically and the patient will be given the diagnosis of familial ALS (FALS) and will be among the 5 to 10% of ALS having genetically determined ALS as listed in the textbooks. However, the other four groups may be given diagnoses of apparent SALS. Epidemiological studies have shown 14 to 23% of recognized FALS and 4 to 7% of apparent SALS cases to carry a *SOD1* mutation. Of the 109 *SOD1* mutations, 17 (V14G, G16S, N19S, E21K, N65S, D76Y, H80R, N86S, D90A, A95T,

D101N, I113T, V118L, V118KTGPX, E133ΔE, V97L, L144F) have been reported in SALS.

This is best documented for the D90A, the most frequent *SOD1* mutation worldwide. The D90A can be inherited both as a recessive trait with slowly progressing ALS with a uniform phenotype or as a dominant trait with greatly reduced penetrance and variable phenotype and survival time. In Finland (population 5.1 million) alone, there are an estimated 99,000 unaffected carriers of the D90A *SOD1* allele. A recent global haplotype study has shown that *all* reported ALS cases with the D90A had a single common founder approximately 18,000 years ago.<sup>3</sup> The third most common *SOD1* mutation is the I113T, which has been found both in families with complete penetrance as well as in apparently SALS cases in the United States. A haplotype study of Scottish SALS and recognized FALS cases with I113T showed them all to have a common ancestor.<sup>4</sup> It is our experience that in ALS-*SOD1* families with diminished penetrance the unaffected transmitting individual is often an elderly woman with affected sons. This is being further studied in ongoing epidemiological studies in Canada and Scandinavia.

We have found an apparent SALS case with N19S: a 77-year-old childless Italian woman developed sudden paresis in the hands with fast dissemination to the rest of the body. The patient died 15 months after onset. Her father had died at age 85 years of a heart disease, her mother at age 78 years of cancer, and a sibling at age 65 years of cancer. The sister had three children 60, 55, and 52 years old without ALS and none of them carried the mutation. The N19S were not found among 120 unrelated Italian controls.

The collective results suggest the existence of a trigger factor in ALS associated with *SOD1* gene mutations. Elucidating this factor would have immense importance, in particular, to the unaffected carriers of *SOD1* gene mutations. It would be interesting to learn what genetic counseling the authors<sup>1</sup> have provided to the seven asymptomatic N19S carriers of their index N19S case.

In this context, it should be recognized that in 1848 F. A. Aran depicted the existence of familial motor neuron disease with reduced disease penetrance.<sup>5</sup>

<sup>1</sup>Department of Clinical Neuroscience, Umeå University, Umeå, Sweden; <sup>2</sup>Laboratory of Molecular Genetics, OIRM-Sant'Anna, Turin, Italy; <sup>3</sup>The Neuromuscular Diseases Unit, Vancouver Hospital, Vancouver, British Columbia, Canada; and <sup>4</sup>Department of Neuroscience, University of Turin, Italy

### References

- Mayeux V, Corcia P, Besson G, et al. N19S, a new *SOD1* mutation in sporadic ALS: no evidence for disease causation. *Ann Neurol* 2003;53:815–818.