

nant form of vanishing white matter-like leukoencephalopathy” creates unnecessary confusion.⁵ We propose to reserve the term *vanishing white matter* for patients who have confirmed mutations in one of the eIF2B genes.⁵ Alternatively, the term *eIF2B-related disorder* can be used for those patients instead. In non-eIF2B-related “vanishing” of cerebral white matter, we would prefer to use the more noncommitted term *cystic leukoencephalopathy of unknown origin*.

As soon as the genes for “autosomal dominant leukodystrophy” (ADLD), “pigmentary orthochromatic leukodystrophy” (POLD) and “hereditary diffuse leukoencephalopathy with spheroids” (HDLS) have been found, genetic analysis will confirm whether the patient who Labauge and colleagues⁴ described is suffering from either one of these disorders.

Department of Pediatrics/Child Neurology, VU University Medical Center, Amsterdam, the Netherlands

References

1. van der Knaap MS, Kamphorst W, Barth PG, et al. Phenotypic variation in leukoencephalopathy with vanishing white matter. *Neurology* 1998;51:540–547.
2. van der Knaap MS, Leegwater PA, Könst AA, et al. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. *Ann Neurol* 2002;51:264–270.
3. van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. *Lancet Neurol* 2006;5:413–423.
4. Labauge P, Fogli A, Castelnovo G, et al. Dominant form of vanishing white matter-like leukoencephalopathy. *Ann Neurol* 2005; 58:634–639.
5. van der Knaap MS, Scheper GC. Non-eIF2B-related cystic leukoencephalopathy of unknown origin. *Ann Neurol* 2005;58:724.

DOI: 10.1002/ana.21003

Reply

Louis Ptacek, MD,^{1,2} Arnulf H. Koepfen, MD,³ and Ying-Hui Fu, PhD¹

We appreciate the letter of Labauge and colleagues regarding pathological findings in childhood ataxia with central nervous system hypomyelination or vanishing white matter disease (CACH/VWM) and the challenges of clinical classification. The decreased number and abnormal morphology of astrocytes are distinguishing features of a small subset of leukodystrophies, and it appears that the autonomic signs may allow accurate distinction of autosomal dominant leukodystrophy (ADLD)¹ from CACH/VWM. Given some of the similarities, it is interesting to speculate whether ADLD and some idiopathic CACH/VWM (ie, without mutations in known genes) might be allelic disorders (given that 10–20% of CACH/VWM patients do not have recognized mutations in genes encoding eIF2B subunits). We have recently identified ADLD to result from lamin B1 gene duplications.² This hypothesis can thus be easily tested. The clinical picture of ADLD mutation carriers is extremely homogeneous. Therefore, if some idiopathic leukodystrophies do result from lamin B1 mutations, we expect they would not result from duplications but from other mutations (eg, null or missense).

It is exciting that so much progress has been made in molecular characterization of many leukodystrophies. Ultimately, some of these genes, and the proteins they encode (particularly in the adult-onset leukodystrophies), are likely to converge in pathways critical for myelin maintenance and repair. Understanding of these pathways will ultimately result in novel targets for development of better therapies for leukodystrophy patients.

¹Department of Neurology, University of California, San Francisco, CA, ²Howard Hughes Medical Institute, University of California, San Francisco, CA, and ³VA Medical Center and Department of Neurology, Albany Medical College, Albany, NY

References

1. Coffeen C, McKenna C, Koepfen A, et al. Genetic localization of an autosomal dominant leukodystrophy mimicking chronic progressive multiple sclerosis to chromosome 5q31. *Hum Mol Genet* 2000;9:787–793.
2. Padiath QS, Saigoh K, Schiffmann R, et al. Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 2006;38:1114–1123.

DOI: 10.1002/ana.21005

B Lineage Cells in Inflammatory Central Nervous System

Howard L. Lipton, MD

A significant component of the scholarly review by Meinl and colleagues¹ on B cells in the inflammatory central nervous system focuses on oligoclonal bands (OCBs) in multiple sclerosis (MS). The initial sentence, “For decades OCB have been recognized as a key immunopathological feature of MS and OIND,”¹ is not supported by scientific data. The presence in cerebrospinal fluid immunoglobulin of functional and antibody activities has been conflated with OCB, but the oligoclonal IgG in MS has not been shown to have demyelinating activity or to be directed against myelin or MOG. This statement also belies the fact that OCBs are a diagnostic “marker” for MS.

Thus, there is no evidence that OCBs play an effector role in myelin breakdown in MS. However, at least four laboratories have provided evidence that OCBs consist of overrepresented IgG molecules with features of an antigen-driven response, most likely from the persistence of viral or possibly self antigens in the CNS,^{2–7} as reviewed by Meinl and colleagues.¹ These data suggest that this response is dynamic, that is, constantly stimulated and changing. The recent finding in MS cerebrospinal fluid that the majority of B cells have a phenotype of memory B cells and short-lived plasma blasts whereas plasma cells were largely absent supports this notion⁶; however, further such studies are needed. In addition, it will be important to confirm by single-cell sequence analysis in individual MS patients over time that the IgGs produced by B lineage cells undergo constant modification, rather than emanate from long-lived plasma cells independent of antigen, as mentioned in Meinl and colleagues’ review.¹ The presence of long-lived plasma cells in the absence of antigen occurs through polyclonal activation of memory B

cells in bone marrow (and possibly in inflammatory sites) (reviewed by Colombo and colleagues⁷); but because this type of response occurs at very low frequencies systemically, it appears unlikely to account for the abundance of OCBs in MS cerebrospinal fluid.

*Departments of Neurology and Microbiology-Immunology,
University of Illinois at Chicago, Chicago, IL*

References

1. Meinl E, Krumbholz M, Hohlfeld R. B lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. *Ann Neurol* 2006;59:880–892.
2. Owens GP, Kraus H, Burgooon MP, et al. Restricted use of VH4 germline segments in an acute multiple sclerosis brain. *Ann Neurol* 1998;43:236–243.
3. Qin Y, Duquette P, Zhang Y, et al. Clonal expansion and somatic hypermutation of Vh genes of B cells from cerebrospinal fluid in multiple sclerosis. *J Clin Invest* 1998;102:1045–1050.
4. Baranzini SE, Jeong MC, Butunoi C, et al. B cell repertoire diversity and clonal expansion in multiple sclerosis brain lesions. *J Immunol* 1999;163:5133–5144.
5. Colombo M, Dono M, Gazzola P, et al. Accumulation of clonally related B lymphocytes in the cerebrospinal fluid of multiple sclerosis patients. *J Immunol* 2000;164:2782–2789.
6. Owens GP, Ritchie AM, Burgooon MP, et al. Single-cell repertoire analysis demonstrates that clonal expansion is a prominent feature of the B cell response in multiple sclerosis cerebrospinal fluid. *J Immunol* 2003;171:2725–2733.
7. Colombo M, Dono M, Gazzola P, et al. Maintenance of B lymphocyte-related clones in the cerebrospinal fluid of multiple sclerosis patients. *Eur J Immunol* 2003;33:3433–3438.

DOI: 10.1002/ana.20964

Reply

Edgar Meinl, MD, Markus Krumbholz, MD,
and Reinhard Hohlfeld, MD

The presence of oligoclonal bands (OCBs) is one criterion to establish the diagnosis of multiple sclerosis (MS). This does not mean that the OCBs are involved in the demyelinating process; we stated in Table 6 of our article¹ that the specificity of OCBs in MS is unknown. We completely agree with Dr. Lipton and see no contradiction to our review.

We would like to make specific statements in response to three other points raised by Dr. Lipton. First, although clonal expansion of B cells in the cerebrospinal fluid (CSF) and within the lesions in MS has been shown by different laboratories (see our review¹), a direct linkage between clonally expanded B-lineage cells (as detected by analysis of rearranged immunoglobulin [Ig] genes) and OCBs (proteins)

has not been formally shown in any of the studies. A future challenge for researchers will be to identify the Ig proteins that are encoded by clonally expanded B-lineage cells and determine whether they are included in the OCBs.

Second, although there is consensus that B cells in the CSF have a memory phenotype, it is, as we reviewed,¹ not settled whether the Ig-producing cells in the CSF of MS patients are (presumably short-lived) plasmablasts^{2,3} or (presumably long-lived) plasma cells.⁴ Plasmablasts disappear in the CSF in neuroborreliosis after resolution of infection, whereas these cells were present in high numbers throughout the disease course in MS.² This indicates that, in neuroborreliosis, the presence of plasmablasts in the CSF is driven by antigen. Whether the plasmablasts in the CSF of MS patients are also antigen driven or rather the consequence of a special B-cell-fostering environment in MS is unclear. We proposed four possible pathways leading to plasmablasts in the central nervous system, two of which are antigen driven.¹

Third, Manz and colleagues nicely explained the concept of long-lived plasma cells as a source for persisting Ig.⁵ This concept implies that plasma cells keep producing Ig independent of the antigen and independent of a polyclonal activation, provided they find a survival niche. Such survival niches are typically found in the bone marrow.⁵ We proposed that the inflamed central nervous system of MS patients also provides a survival niche for long-lived plasma cells, which are presumably the source of the OCBs.¹

*Department of Neuroimmunology, Max-Planck-Institute of
Neurobiology, Martinsried, and Institute for Clinical
Neuroimmunology, Ludwig-Maximilians-University, Munich,
Germany*

References

1. Meinl E, Krumbholz M, Hohlfeld R. B lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. *Ann Neurol* 2006;59:880–892.
2. Cepok S, Rosche B, Grummel V, et al. Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. *Brain* 2005;128:1667–1676.
3. Krumbholz M, Theil D, Cepok S, et al. Chemokines in multiple sclerosis: CXCL12 and CXCL13 up-regulation is differentially linked to CNS immune cell recruitment. *Brain* 2006;129:200–211.
4. Corcione A, Casazza S, Ferretti E, et al. Recapitulation of B cell differentiation in the central nervous system of patients with multiple sclerosis. *Proc Natl Acad Sci U S A* 2004;101:11064–11069.
5. Manz RA, Hauser AE, Hiepe F, et al. Maintenance of serum antibody levels. *Annu Rev Immunol* 2005;23:367–386.

DOI: 10.1002/ana.21004