the diagnostic pathology journal DIAGNOSTIC PATHOLOGY

Martin Berghoff, diagnostic pathology 2015, 1:87
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2015-1:87

Letter to the Editor

Success and failure in translation of findings from experimental autoimmune encephalomyelitis to multiple sclerosis

Martin Berghoff*, MD

Department of Neurology, University of Giessen, Klinikstrasse 33, 35385 Giessen, Germany

*Corresponding author Email: martin.berghoff@neuro.med.uni-giessen.de

Abstract

Despite the differences between multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE), most of the knowledge on immune-mediated tissue damage in MS is based on data from EAE. Immune response–modifying therapies such as TNFα inhibitors, glatiramer acetate (GA) or natalizumab have been studied in rodents and have been translated into treatment for patients with varying success. In humans treatment with an anti TNF monoclonal antibody or a recombinant TNF receptor Ig fusion protein resulted in enhanced inflammation. In contrast, findings from GA or natalizumab have been successful in human translation. Findings of EAE studies should be interpreted carefully and should be confirmed using substances (proof of principle). Only if successful, these substances should be studied in humans.

Keywords: Encephalomyelitis; Translational Pathology; Neurology; Autoimmune Disorders; Therapeutic Strategies; Knockout Mice.

Dear Dr. Kayser,

On behalf of the international conference on tissue - based diagnosis - the past and the future, in Bad Duerkheim, I want to inform you and your colleagues about the value of tissue investigations to achieve and confirm the diagnosis multple sclerosis in clinically symptomatic patients.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS). It is estimated that more than 120.000 subjects are affected in Germany. There are different subtypes of MS such as relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) or primary progressive MS (PPMS). Signs and symptoms of MS vary and may include somatosensory, pyramidal-motor and visual manifestations. The key pathological features found in MS lesions are a) inflammation, b) demyelination, c) axonal degeneration and d)

Martin Berghoff, diagnostic pathology 2015, 1:87
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2015-1:87

gliosis. The lesions are heterogeneous in size and location, and in the relative proportion of the pathological features [Lucchinetti *et al.* 2000].

MS is diagnosed applying McDonald diagnostic criteria [Polman *et al.* 2011], which are based on the clinical presentation, and/or evidence of dissemination of lesions in time and space on MRI. T2 lesions are typically located periventricular, juxtacortical, infratentoriell or in the spinal cord. T2 lesions are unspecific; they may represent inflammation, demyelination or axonal degeneration. McDonald criteria have helped to facilitate early diagnosis of MS with a high degree of sensitivity and specificity, and have resulted in early treatment of RRMS.

In neuropathology studies four patterns of demyelination could be differentiated [Lucchinetti *et al.* 2000]. Pattern I is T cell-mediated, pattern II is both T cell- and B cell-mediated, and patterns III and IV are caused by dysfunction of oligodendrocytes. Demyelination can be found both in the white and grey matter of the CNS [Lassmann *et al.* 2007], during acute attacks of myelin destruction axons degenerate. The composition of MS lesions may vary within patients. In comparison with the high number of patients with MS, the number of biopsy or autopsy samples is low. Brain or spinal cord tissue is often taken from selected, untypical cases with suspected diseases such as brain tumor, and there is a lack of longitudinal data. The findings from neuropathology studies may not accurately reflect the pathology of MS.

Over the last few decades, the animal model experimental autoimmune encephalomyelitis (EAE) has been used increasingly to characterize the underlying pathogenic immune mechanisms involved in MS [Gold *et al.* 2006]. The model most often used today is MOG_{35-55} induced EAE in C57BL/6, these mice present with a chronic-progressive disease course with demyelination and axonal damage similar to human MS. In contrast to humans, MOG_{35-55} induced EAE is not a spontaneous disease and pertussis toxin is required to induce it. Despite the differences between MS and its model, most of the knowledge on immune-mediated tissue damage in MS is based on data from EAE and not on neuropathology or MRI findings in humans. Based on basic immune mechanisms found in EAE models, immune response–modifying therapies such as TNFα inhibitors, glatiramer acetate (GA) or natalizumab have been studied in rodents and have been translated into treatment for patients with varying success.

TNFα, a cytokine with both pro- and anti-inflammatory properties, is known to play a role in the pathology of MS and EAE. TNF-blockade inhibits the development of EAE [Selmaj *et al.* 1991]. Despite this promising anti-inflammatory finding in the model, treatment with an anti TNF monoclonal antibody [van Oosten *et al.* 1996] or a recombinant TNF receptor Ig fusion protein [The Lenercept Multiple Sclerosis Study Group 1999] resulted in enhanced inflammation. The findings in humans suggest that TNF plays an important role in limiting inflammation in MS. The two TNF receptors mediate opposing effects; blockade of TNF/TNFR2 pathway may have caused less apoptosis, ongoing inflammation and increased clinical disease activity.

Martin Berghoff, diagnostic pathology 2015, 1:87
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2015-1:87

Findings from two substances used in EAE have been successful in human translation. Glatiramer acetate (GA; previously known as Cop 1) was initially developed to induce EAE, however, in studies it had an opposite effect [Teitelbaum *et al.* 1971]. Proposed mechanisms include interference with antigen presentation, cytokine shift or induction of immunological tolerance. In the pivotal study [Johnson *et al.* 1995] subcutaneous GA reduced relapses by 29%, there was no significant effect on disease progression in this study. GA is a widely used substance in the treatment of mild or moderate courses of RRMS. VLA-4 (*α4β1* integrin), expressed on the surface of lymphocytes, mediates lymphocyte migration into the CNS. In an EAE study application of an antibody against VLA-4 suppressed EAE [Yednock *et al.* 1992]. Natalizumab binds to the *α4* subunit of *α4β1* and *α4β7* integrins and blocks binding of lymphocytes to VCAM-1 on the blood-brain barrier. In the pivotal study natalizumab reduced relapses by more than 60% and it also delayed disease progression [Polman *et al.* 2006]. Natalizumab is the most important substance in the treatment of severe courses of RRMS. It is associated with a severe opportunistic viral infection causing progressive multifocal leukoencephalopathy (PML). Up to date more than 500 subjects were affected by PML and more than 100 subjects died from the infection. In general, natalizumab is a good example of concordance between EAE and MS. It is, however, also an example of the risk of transferring all aspects of a drug treatment from EAE to MS, in particular in case of complications only affecting humans.

In summary, EAE is useful to study basic mechanisms of inflammation and tissue destruction in the CNS. Results from EAE studies applying GA and natalizumab have been successful in human translation. There is no perfect model of MS (or other diseases), there are relevant differences between human disease and EAE, and discordant findings between MS and models are likely to be due to these differences. Still there is an urgent need for substances for the treatment of progressive MS, up to date findings from EAE studies could not be translated successfully to progressive subtypes of MS. To improve translation, findings of EAE studies should be interpreted carefully, they should be confirmed using substances (proof of principle) and only if successful, these substances should be studied in humans.

References:

[1]. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1999; 53: 457-465.

[2]. Gold R, Linington C, Lassmann H. Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. Brain 2006; 129: 1953-1971.

Martin Berghoff, diagnostic pathology 2015, 1:87
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2015-1:87

[3]. Johnson KP, Brooks BR, Cohen JA *et al*. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995; 45: 1268-1276.

[4]. Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. Brain Pathol 2007; 17: 210-218.

[5]. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000; 47: 707-717.

[6]. Polman CH, O'Connor PW, Havrdova E *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899-910.

[7]. Polman CH, Reingold SC, Banwell B *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292-302.

[8]. Selmaj K, Raine CS, Cross AH. Anti-tumor necrosis factor therapy abrogates autoimmune demyelination. Ann Neurol 1991; 30: 694-700.

[9]. Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. Eur J Immunol 1971; 1: 242-248.

[10]. van Oosten BW, Barkhof F, Truyen L *et al*. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology 1996; 47: 1531-1534.

[11]. Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. Nature 1992; 356: 63-66.