Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 22
Sofia ● 2015

Clinical Case of a Patient with RRMS and Acute Inflammatory Response Following Vaccination against Tetanus

V. Kolyovska[1], D. Maslarov[2]

[1]Institute of Experimental Morphology, Pathology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia
[2]Medical University of Sofia, Neurology Clinic, First MHAT – Sofia

Multiple sclerosis (MS) is an inflammatory disease in which the myelin sheaths around the axons of brain and spinal cord's neurons are damaged by autoantibodies, resulting in demyelination and scarring. The aim of this investigation was to show clinical significance of the tetanus vaccination and risk of autoimmune reactions in patients with MS. The risks associated with a number of vaccines have been investigated in patients with MS. Many patients with MS received immunosuppressive or immunomodulatory therapy, which could make them more susceptible to infectious diseases and might also affect their ability to respond to immunization. Here, we review the indications for and possible adverse effects of vaccines in patients with MS, and address issues of vaccination in the context of immunomodulatory therapy for MS. It is recommended that vaccines in patients with long time suppressed immune system to be applied very carefully, only if there is proven necessity and close monitoring.

Key words: multiple sclerosis, multiple sclerosis treatment, Glatiramer acetate, tetanus vaccination, autoimmune reaction.

Introduction

Multiple sclerosis (MS) is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons. Initially, inflammation is transient and remyelination occurs but is not durable. Hence, the early course of disease is characterized by episodes of neurological dysfunction that usually recover. However, over time the pathological changes become dominated by widespread microglial activation associated with extensive and chronic neurodegeneration, the clinical correlate of which is progressive accumulation of disability. Preclinical investigations show abnormalities that indicate the distribution of inflammatory lesions and axonal loss (MRI); interference of conduction in previously myelinated pathways (evoked electrophysiological potentials); and intrathecal synthesis of oligoclonal antibody (examination by lumbar puncture of the cerebrospinal fluid) [2].

The initial MS therapeutic strategies were directed at immune modulation and inflammation control. Disease-modifying drugs (DMDs) require long-term, regular injec-

tion or monthly parenteral infusions, which may impact the patient's compliance. The aim is to prevent demyelination and to reduce axonal loss. During the different MS phases patients use various drugs: in attacks – Corticosteroids; immunomodulators – Interferon beta-1a, Interferon beta-1b (INFs), Glatiramer acetate and Fingolimod [11].

Glatiramer acetate (licensed in 1996) is an immunomodulatory drug currently used to treat relapsing-remitting MS (RRMS). It is a random polymer of four amino acids found in myelin basic protein, namely glutamic acid, lysine, alanine, and tyrosine, and may work as a decoy for the immune system. Glatiramer acetate (GA) is approved by the Food and Drug Administration (FDA) for reducing the frequency of relapses, but not for reducing the progression of disability. GA has also been shown to limit the formation of new MS-related lesions in the central nervous system (CNS) and to reduce brain atrophy [10]. The role of vaccinations in risk of developing MS or in risk of relapse has not been well established. The aim of the studies was to estimate the effect of immunizations and the risk of developing MS in adults as well as in subsequent risk of relapse [4].

Several studies have demonstrated an effect of GA on T regulatory cells (Tregs), which are potent immunosuppressor cells pivotal in the maintenance of self-tolerance. However, the role of this cell population in the therapeutic effect of GA has not been clarified. To clarify the requirement of Treg cells in the therapeutic activity of GA in an animal model of multiple sclerosis is experimental autoimmune encephalomyelitis (EAE) was used. GA treatment induces elevation of T-regulatory cells. Selective depletion of these Tregs reduces but does not eliminate the ability of GA to ameliorate EAE. These findings support the role of Tregs, but not in an exclusive fashion, in the therapeutic effect of GA. [1].

Materials and Methods

The patient is a 40-year-old woman. MRI performed with 20 years confirmed clinical diagnosis of MS, relapsing-remitting variant, satisfying McDonald MRI criteria, with assigned level 1.5-2 Kurtzke Disability Status. The patient was on therapy with GA from ten years. From 2005 until year 2014 the patient has been in a remission with two or three weak exacerbations.

During the normal procedure with GA patient was bitten by a street dog. Doctors have implemented vaccination with tetanus vaccine. Some time thereafter (2-3 weeks) suddenly appeared bumps and severe, excruciating pain in the joints. Ultrasound appeared effusion of synovial fluid in the joints of the knees, ankles and wrists. Expressed were effusions on superolateral bursae and soft proliferation of the synovial membrane. The complete blood count of the patient is normal. The level of C-reactive protein (CRP), a marker of long-term inflammatory response in the body is normal – less than 10 mg/L (SI). Symptomatic treatment with medication Movalis (15 mg) was appointed for ten days. Then, there was a sharp decline in the swelling of the joints. Doubts for gout were also rejected. Most likely acute pain, swelling and indispositions in the body are available because of suppressed immune system many years. Perhaps this is a reaction of poorly purified proteins in the vaccine.

The study was conducted in compliance with the principles of the Declaration of Helsinki 1964 and its amendments (Tokyo 1975, Venice 1983, Hong Kong 1989). Similar studies have not been performed so far.

In the current investigation, clinical studies were focused on the type, morphology and evolution of MS lesions using conventional MRI in a patient with RRMS before GA treatment (**Fig. 1**) and during the therapy (**Fig. 2**). MRI was designed to assess the frequency, extent, and rate of cortical lesions formation in RRMS and their relationship

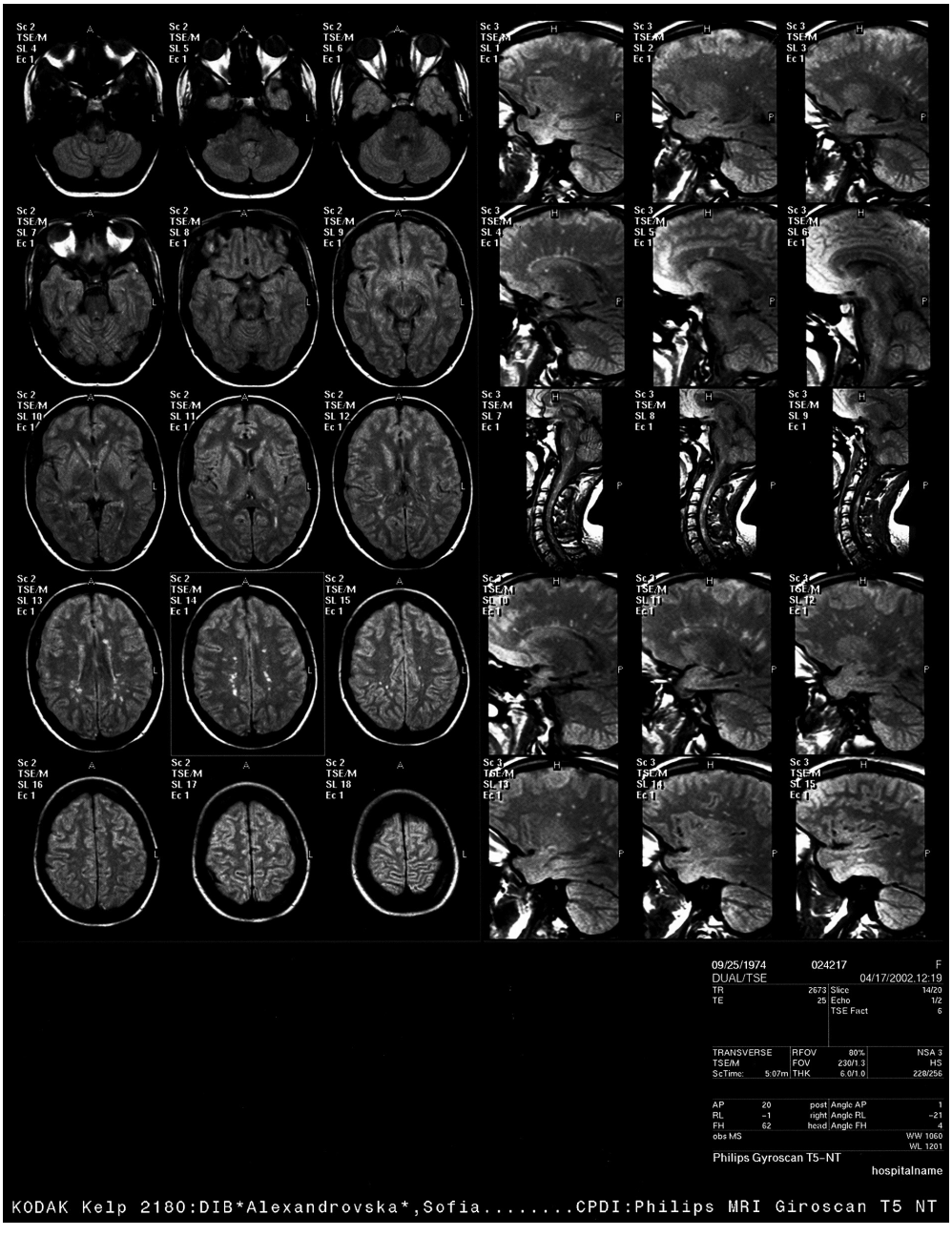

Fig. 1. MRI in a patient with RRMS before Glatiramer acetate treatment

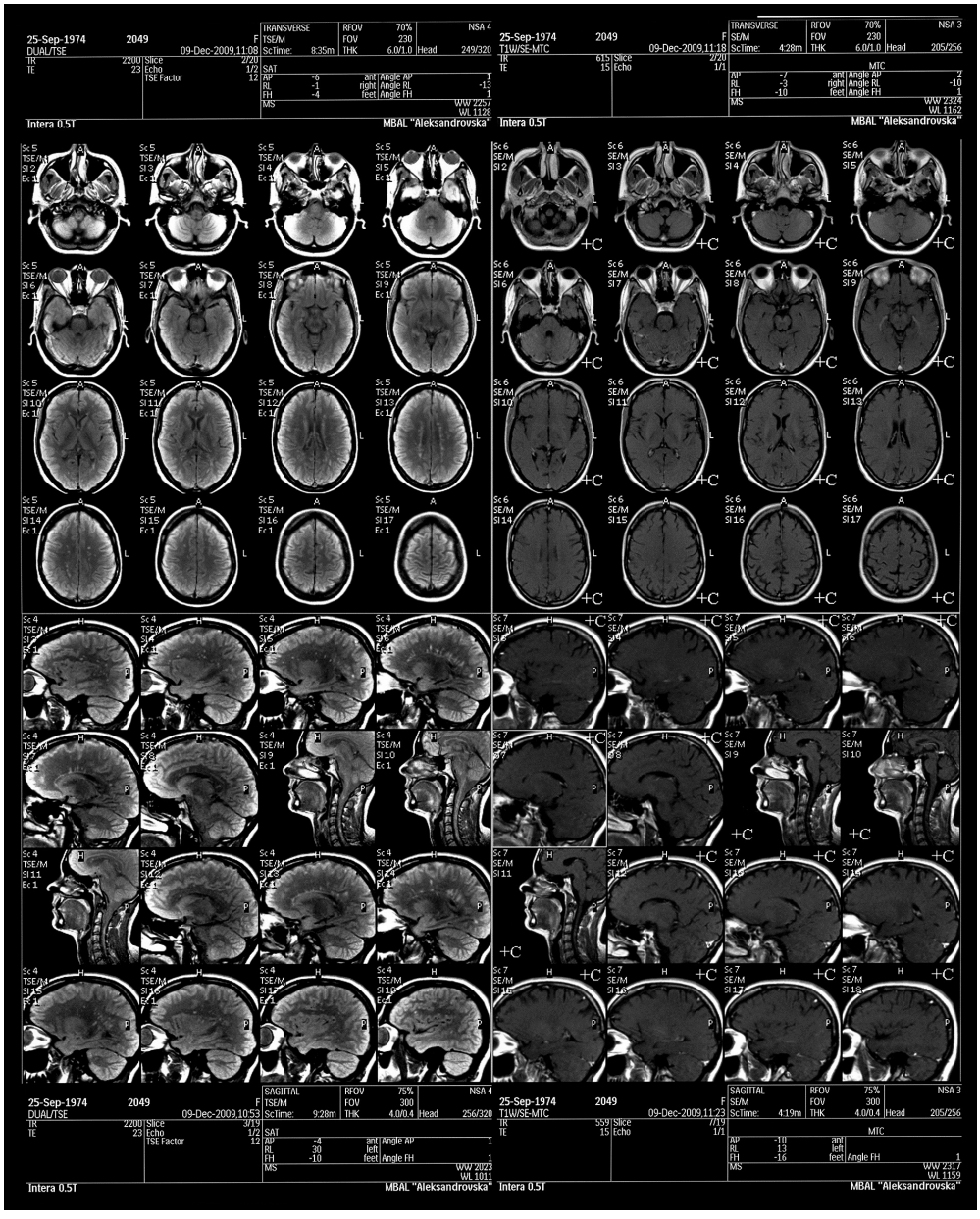

Fig. 2. MRI in a patient with RRMS after Glatiramer acetate treatment

with T2 lesion volume, white matter atrophy, and disability. Regrettably, MRI has not been investigated after the inflammatory response.

Results

MRI results from a longitudinal study

Year 2002 – MRI brain and spinal cord in axial and sagittal planes

Multiple, predominantly small hyperintense foci in the brain white matter located bilaterally periventricularly and subcortically towards the convexity, in the basal ganglia and capsula interna, in all parts of corpus callosum, in the cerebellum, pons, craniospinal junction and along the cervical spinal cord. These changes are usually seen in a demyelinating process such as MS with cranial and spinal involvement with corresponding clinical and immunologic evidence (**Fig. 1**).

Year 2005 – Brain MRI in axial plane and cervical spine in sagittal plane

Compared to previous MRI study from 2002 – no dynamic changes; no evidence of disease progression based on "lesion load on T2".

Year 2009 – MRI brain and spinal cord in axial and sagittal planes with gadolinium contrast enhancement (0.1 mmol Gd/kg)

Compared to previous MRI findings from 2005 – no evidence of disease progression based on "lesion load on T2". Intact blood-brain and blood-spinal fluid barriers (**Fig. 2**).

Year 2011 – MRI brain: T2 imaging in axial and sagittal planes, FLAIR axial and T1 sagittal planes

Subarachnoid space and brain ventricles – normal. Supra- and subtentorial hyperintense foci documented previously on T2 and FLAIR imaging from 2009 persist. Hyperintense foci noted in cervical cord at C2 level. Pontocerebellar angles appear normal. Brain ventricular system – normal shape, size and location. No evidence of MRI findings progression compared to MRI study from 2009 – cerebrospinal demyelinating process.

The fact that there is no progression on MRI imaging findings from 2005 until 2012 based on brain "T2 lesion load" suggests the protective role of GA treatment.

Discussion

Vaccination against infection becomes important in patients with neuromyelitis optica spectrum disorder (NMOSD) because they are at an increased risk of infection due to long-term immunosuppressive therapy. However, it is unclear whether NMOSD patients under immunosuppression therapy show proper antibody formation after vaccination. Thus the antibody formation after influenza A (H1N1) vaccination in patients with NMOSD receiving rituximab was evaluated [9]. This study shows a severely hampered humoral immune response to H1N1 influenza vaccine in patients with NMOSD treated with rituximab, although the vaccination itself is safe in these patients [9].

Bacterial and viral infections have been shown to induce relapses and accelerate the progression of MS. Vaccination to prevent communicable disease in such patients is, therefore, of key importance. Reports of potentially detrimental effects of immuni-

zation on the course of MS, however, have prompted patients and physicians to adopt a cautious attitude towards the use of vaccines. The risks associated with a number of vaccines have been investigated in patients with MS. Many patients with MS receive immunosuppressive or immunomodulatory therapy, which could make them more susceptible to infectious diseases and might also affect their ability to respond to immunization. The researchers reviewed the indications for and possible adverse effects of vaccines in patients with MS, and address issues of vaccination in the context of immunomodulatory therapy for MS [12]. Tetanus vaccination is associated with a low risk of multiple sclerosis in healthy people [6].

That is not indicative of patients with permanently suppressed immunity as patients treated with GA. The question of a connection between vaccination and autoimmune illness (or phenomena) is surrounded by controversy. A heated debate is going on regarding the causality between vaccines, such as measles and anti-hepatitis B virus (HBV), and MS. Brain antibodies as well as clinical symptoms have been found in patients vaccinated against those diseases [13].

Post-vaccination acute disseminated encephalomyelitis (ADEM) has been associated with several vaccines such as rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, and the Hog vaccine. Researchers review ADEM with particular emphasis on vaccination as the precipitating factor [7]. In the current study investigations were focused on the tetanus vaccination and risk of autoimmune reactions in patients with RRMS. The aim of the MS treatment is to prevent demyelination and to reduce axonal loss. Vaccination against hepatitis B (HB), influenza, tetanus, measles, or rubella is not associated with an increased risk of multiple sclerosis or optic neuritis [3].

This is a statement in healthy subjects. In the cases of patients with permanently suppressed immune response the reaction of vaccination is not the same. Several hundred cases of an acute central demyelinating event following HB vaccination were reported to the pharmacovigilance unit, leading to a modification of vaccination policy in the schools and the initiation of several studies designed to examine the possible relationship between the vaccine and the central demyelinating events. The results of these studies failed to establish the causality of the HB vaccine. Nevertheless, molecular mimicry between HB antigen(s) and one or more myelin proteins, or a non-specific activation of autoreactive lymphocytes, would constitute possible pathogenetic mechanisms for these adverse neurological events [5].

Farez and Correale [4] suggest that no significant change in the risk of developing MS after vaccination was found for BCG, Hepatitis B, Influenza, Measles-Mumps-Rubella (MMR), Polio and Typhoid fever. They found decreased risk of developing MS for Diphtheria and Tetanus. Influenza immunization was also associated with no change in risk of MS relapse. Risk of developing multiple sclerosis remained unchanged after BCG, Hepatitis B, Influenza, MMR, Polio and Typhoid fever immunization, whereas diphtheria and tetanus vaccination may be associated with a decreased risk of MS. Further research is needed for the remaining vaccines [4].

Kappos et al. [8] evaluated the immune responses in Fingolimod-treated patients with MS against influenza vaccine (to test for responses against anticipated novel antigens in seronegative patients) and recall (tetanus toxoid booster dose) antigens. Most Fingolimod-treated patients with MS were able to mount immune responses against novel and recall antigens and the majority met regulatory criteria indicating seroprotection. However, response rates were reduced compared with placebo-treated patients. This should be kept in mind when vaccinating patients on Fingolimod [8]. In some patients with MS receiving immunizations, concurrent Fingolimod treatment in comparison to placebo decreases vaccination-induced immune responses.

Conclusion

Two problems must be considered in regard to the relationship between vaccinations and MS: Do vaccinations favor the first attack of MS? Do they increase the short- or long-term risk in patients with known disease? Answers to these questions are difficult due to the paucity of reported cases, our ignorance of the precise frequency of neurological adverse events in vaccines based on prospective studies, and finally by the lack of a well established pathophysiology.

In most instances, the role of the vaccine is based on a temporal link between the injection and the onset of neurological disease, and more rarely to a positive reintroduction. The mechanism (or mechanisms) of autoimmune reactions following immunization has not yet been elucidated. One of the possibilities is molecular mimicry; when a structural similarity exists between some viral antigen (or other component of the vaccine) and a self-antigen. This similarity may be the trigger to the autoimmune reaction. Other possible mechanisms are discussed. Even though the data regarding the relation between vaccination and autoimmune disease is conflicting, it seems that some autoimmune phenomena are clearly related to immunization (e.g. Guillain-Barre syndrome).

It is recommended that vaccines in patients with long time suppressed immune system to be applied very carefully, only if there is proven necessity and close monitoring. As their immune system is permanently suppressed, it does not respond in the way that reacts in healthy people.

References

1. **Aharoni, R., T. Feferman, D. Bar Lev, G. Shakhar, M. Sela, R. Arnon.** The role of T regulatory cells in the therapeutic effect of glatiramer acetate in experimental autoimmune encephalomyelitis. – J. Multiple Sclerosis, **20**, 2014, 326.
2. **Compston, A., A. Coles.** Multiple sclerosis. – Lancet, **372**(9648), 2008, 1502-1517.
3. **DeStefano, F**., **T. Verstraeten**, **L. Jackson**, **C. Okoro**, **P. Benson**, **S. Black,** H. **Shinefield**, **J. Mullooly**, **W. Likosky**, **R. Chen**. Vaccinations and risk of central nervous system demyelinating diseases in adults. – Arch. Neurol., **60**(4), 2003, 504-509.
4. **Farez, M., J. Correale.** Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. – J. Neurol., **258**(7), 2011, 1197-1206.
5. **Gout, O.** Vaccinations and multiple sclerosis. – Neurol. Sci., **22**(2), 2001, 151-154.
6. **Hernán, M., A. Alonso, S. Hernández-Díaz.** Tetanus vaccination and risk of multiple sclerosis: a systematic review. – Neurology, **67**(2), 2006, 212-215.
7. **Huynh, W., D. Cordato, E. Kehdi, L. Masters, C. Dedousis.** Post-vaccination encephalomyelitis: literature review and illustrative case. – J. Clin. Neurosci., **15**(12), 2008, 1315-1322.
8. **Kappos, L., M. Mehling, R. Arroyo, G. Izquierdo, K. Selmaj, V. Curovic-Perisic, A. Keil, M. Bijarnia, A. Singh, P. von Rosenstiel.** Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. – Neurology, **84**(9), 2015, 872-879.
9. **Kim, W., S. H. Kim, S. Y. Huh, S. Y. Kong, Y. J. Choi, H. J. Cheong, H. J. Kim.** Reduced antibody formation after influenza vaccination in patients with neuromyelitis optica spectrum disorder treated with rituximab. – J. Eur. Neurol., **20**(6), 2013, 975-980.
10. **Kolyovska, V., S. Todorov, D. Maslarov.** New perspectives in multiple sclerosis treatment. – Medical Data, **5**(3), 2013, 241-244.
11. **Kolyovska, V., D. Maslarov, I. Dokova, S. Todorov, I. Iliev, S. Engibarov, R. Eneva.** Serum IgG antibodies to GM1, GM3 and GD1a gangliosides in patients with relapsing remitting multiple sclerosis under treatment with Interferon, Glatiramer acetate and Laquinimod – preliminary data. – Acta morphol. et anthropol., **21**, 2015, 62-66.
12. **Löebermann, M., A. Winkelmann, H. Hartung, H. Hengel, E. Reisinger, U. Zettl.** Vaccination against infection in patients with multiple sclerosis. – Nat. Rev. Neurol., **8**(3), 2012, 143-151.
13. **Shoenfeld, Y, A. Aron-Maor.** Vaccination and autoimmunity-'vaccinosis': a dangerous liaison? – J Autoimmun., **14**(1), 2000, 1-10.