Müller. *Neuroimmunol Neuroinflammation* 2018;5:23
DOI: 10.20517/2347-8659.2018.27

Neuroimmunology and Neuroinflammation

Commentary

Open Access

Check for updates

Commentary on "Depression severity and its predictors among multiple sclerosis patients in Saudi Arabia: a cross-sectional study"

Thomas Müller

Department of Neurology, St. Joseph Hospital Berlin - Weissensee, Berlin 13088, Germany.

Correspondence to: Prof. Thomas Müller, Department of Neurology, St. Joseph Hospital Berlin - Weißensee, Gartenstr. 1, Berlin 13088, Germany. E-mail: th.mueller@alexianer.de, thomas.mueller@ruhr-uni-bochum.de

How to cite this article: Müller T. Commentary on "Depression severity and its predictors among multiple sclerosis patients in Saudi Arabia: a cross-sectional study". *Neuroimmunol Neuroinflammation* 2018;5:23. http://dx.doi.org/10.20517/2347-8659.2018.27

Received: 9 May 2018 **Accepted:** 11 May 2018 **Published:** 7 Jun 2018

Science Editor: Athanassios P. Kyritsis **Copy Editor:** Guang-Zhe Zhu **Production Editor:** Huan-Liang Wu

Multiple sclerosis (MS) is looked upon as chronic autoimmune disease. Current therapeutic research focus on the prevention of relapses in association with morphological magnet resonance imaging (MRI) parameters. This paper again describes that depression is one of the most common symptoms in MS. Components of depression for manifestation in MS are exogenous, such as disability, or endogenous, i.e., due to localisation of lesions, which predispose for onset of depression. This paper points out that depression and related neuropsychiatric symptoms, i.e., apathy and fatigue, should not be underestimated in the clinical maintenance of MS patients. This paper supports the view, that further research is warranted beyond past and future ongoing trials on cognitive deficits, which frequently disregard the impact of apathy and fatigur on standardised neuropsychological testing in association with chronic intake immune system modulating compounds. Therefore it is promising that efforts are undertaken on standardisation of neuropsychological assessment tools, i.e. for cognition, in trials[1], whereas the MiniMental State Examination score have a considerable bias by the educational level of the patient. Clinicians repeatedly point out, that non-cognition related signs are often essential limiting for quality of life. As a result, they investigate the efficacy of already available compounds often in observational or naturalistic small trials, like in this paper. Clinicians point out that non-cognition related signs are often essential limiting for quality of life. As a result, they investigate the efficacy of already available compounds often in observational or naturalistic small trials. These outcomes are frequently considered as less essential by the authorities driven evidence-based-medicine classification of trials. One must consider that most of the used assessment instruments are not objective. They are biased by the attitude and habits of the investigator. One underestimates that the rating situation and the stress for the

© The Author(s) 2018. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

patient often cause an insufficient appraisal of the tested compound.

Nevertheless, it is worth to mention that certain drugs, such as interferons with their flu-like side effect profile and their more frequent application rate, support onset of certain neuropsychiatric symptoms in contrast to glatiramer acetate or compounds with distinct less frequent intake, such as natalizumab, ocrelizumab or cladribin. In this respect, outcomes of Table 6 are of interest in combination with the discussion on the severity of depression in relation to the applied medications. Here the authors conclude that drug side effects may account for the found differences between treatments. This is an important aspect, which leads the way to select medications with a need for less frequent intake, i.e., cladribine or ocrelizumab, in the future. Thus, this paper also emphasizes by circumstantial evidence that not only reduction of the annual relapse rate or MRI changes are important but also the kind of MS treatment for prevention of relapses. Another point is the individually different necessary symptomatic therapy with spasticity ameliorating compounds or cannabis like compounds. Nearly all of them induce fatigue. Moreover, dosing depends on concomitant factors, i.e., body weight, severity of spasticity in relation to the localisation and size of lesions. Therefore, this trial also underlines again that (1) MS therapy is complex, (2) asks for a patient tailored regime particularly in the more advanced stages of the disease, and (3) maintenance of MS patients often faces the additional appearance of various kinds of non-motor symptoms, i.e., depression. There is also hysteria on safety. In the real world, clinical researchers underline the importance of the so-called nocebo-effect. This means that patient experiences a side effect once being informed on its potential occurrence[2,3]. In the clinical research scenario, the side effect profile and the tolerability of a tested immune system modulating compound appears to have more or at least the same importance than its efficacy. In clinical practice however, the application of a compound is often the result of a careful benefit-risk evaluation performed by the prescribing physician and the more and more well informed, mature patient. It is more important to select a therapy for the modulation of the immune system, which is well tolerated and accepted by the individual patients. This also increases the adherence to compound. Particularly, compliance is an important issue in the maintenance of MS patients. Missing adherence may also contribute or trigger the Immune-reconstitution inflammatory syndrome. If it occurs, it will may in turn weaken the confidence of the patient and the physician in the applied compound[4-6].

In contrast, the current artificial clinical study world mostly only focus on relapse prevention and MRI findings. The fancy translational approach to test compounds, which were successful in experimental autoimmune encephalitis models with their focus on relapse prevention by modulation of the immune system only, looks promising, but do not reflect all the therapeutic challenges of clinical practice. The limitation of these experimental models and thus the performed experimental investigations is the focus on the immune system. These models often only mirror mechanisms of neuronal dying based on immunological mechanisms modulated by B- or T-cells. Thus, experimental research neglects that chronic neuroinflammation and associated neurodegeneration may also cause further consequences, such as psychopathological features and personality changes. The register trials often use quality of life scales, which disregard the individually varying, existing capacity of the human brain to compensate these neuropsychiatric events for certain intervals before the clinical onset of initial mild and unspecific symptoms. This so-called “neuroplasticity” phenomenon may also impact the rate of progression and thus differs in an individual different manner. In summary, this heterogeneous and individual different disease progression in combination with relative short trial periods may also contribute to a failure of trials on disease modification, particularly in progressive MS. Mortality or increase of life expectance, caregiver burden or delay of transfer to nursing homes may represent more robust clinical endpoints in terms of disease modification in comparison to the mostly applied expanded disability status scale score or the artificial conversion endpoints from relapse remitting to progressive MS. One must admit that the aforementioned suggested, alternative endpoints would demand longer study durations particularly in the real world, as suggested in this paper. However, the real world finally determines the value of treatment and the efficacy of drugs.

DECLARATIONS

Authors' contributions

Müller T contributed solely to the paper.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2018.

REFERENCES

1. Larner AJ. Correlation or limits of agreement? Applying the Bland-Altman approach to the comparison of cognitive screening instruments. Dement Geriatr Cogn Disord 2016;42:247-54.
2. Kleine-Borgmann J, Bingel U. Nocebo effects: neurobiological mechanisms and strategies for prevention and optimizing treatment. Int Rev Neurobiol 2018;138:271-83.
3. Ren Y, Xu F. How patients be counseled on adverse drug reactions: avoiding the nocebo effect. Res Social Adm Pharm 2018; doi: 10.1016/j.sapharm.2018.04.007.
4. Beran RG, Hegazi Y, Schwartz RS, Cordato DJ. Rebound exacerbation multiple sclerosis following cessation of oral treatment. Mult Scler Relat Disord 2013;2:252-5.
5. Igra MS, Paling D, Wattjes MP, Connolly DJA, Hoggard N. Multiple sclerosis update: use of MRI for early diagnosis, disease monitoring and assessment of treatment related complications. Br J Radiol 2017;90:20160721.
6. Mulero P, Neri MJ, Rodriguez M, Arenillas JF, Téllez N. Immune reconstitution inflammatory syndrome and natalizumab - is it possible before removing the drug? Mult Scler Relat Disord 2014; 3:659-61.