

Multiple sclerosis: Why do we understand so little and are unable to provide meaningful therapy?

Israel Steiner¹, Puiu Nisipeanu² and Itzhak Wirguin³

Departments of Neurology, ¹Hadassah University Hospital, Jerusalem, ²Hillel Yaffe Medical Center, Hadera, and ³Soroka Medical Center, Ben Gurion University, Beer Sheva, Israel

Received 16 March 2005; accepted in final form 20 November 2005

Correspondence and requests for reprints should be addressed to:

Prof. Israel Steiner
Department of Neurology
Hadassah University Hospital
P.O. Box 12000
Jerusalem 91120
Israel
Tel: 972-2-6776952
Fax: 972-2-
E-mail: iSteiner@md2.huji.ac.il

Abstract

Objectives: Despite many years of intensive research, multiple sclerosis (MS) still evades understanding and its treatment remains suboptimal. Our aim in this report is to analyze the reasons for this situation, review the present available therapies and put forward several constructive suggestions.

Methodology: We searched the literature from 1966 to 2005 for relevant articles and chapters. Review articles were also included.

Results: Reasons for the current satelment in the field are the meaninglessly broad spectrum of diagnostic criteria, the inability to define the efficacy of therapies, lack of fulfillment of criteria for an autoimmune condition and the pressure from the biomedical industry.

Conclusions: Clinical criteria for diagnosis should be redefined and the new set of disease classification should be based on disease course; clinical studies should consist of homogenous group of patients and a uniform set of end points to evaluate clinical therapeutic trials should be agreed upon. Most important, a moratorium on the autoimmunity hypothesis in MS will enable to redirect funds for research with lower emphasis on autoimmunity, but rather on novel approaches to the problem.

Key Words

Nervous system, Multiple sclerosis, autoimmunity, experimental allergic encephalomyelitis

Definition of the problem and its scope

Clinical neurology is undergoing a major metamorphosis. Slowly, but in a constantly promising pace, the etiology and pathogenesis of many chronic, genetic or acquired conditions are being elucidated, at least in part due to the revolution in molecular biology. This does, and will pave the way to the development of effective symptomatic, prophylactic and curative therapies. The same applies to acute conditions, such as cerebrovascular disorders and infections, where the spectrum of effective, real time therapeutic measures is likewise steadily enlarging.

Thus, from a frustrating, diagnostic and theoretical profession, neurology is being transformed into an active discipline. Multiple sclerosis (MS), however, remains a condition that has seen no effective change, neither in our understanding of the cause of the disorder, nor in clarifying the mechanisms of tissue destruction. As fifty years ago, the neurologist cannot offer much more than diagnosis, empathy and therapies with a disappointingly modest effect.

MS is a disease of the young adult. The nervous system

is progressively destroyed leaving some of the victims incapacitated for life. The leading and practically dogmatic hypothesis has been and is that the pathogenesis of MS is autoimmune and hence that its symptoms and progression could be ameliorated by immuno-suppressive or immuno-modulating modalities. Nevertheless, while the field of neuroimmunology has prospered, drawing extensive funds, and many talented basic scientists and clinicians have built their academic careers in the arena of immune-mediated mechanisms of tissue damage in MS and on promoting therapies, only a very limited progress has been made both towards understanding MS or towards developing a rational and effective therapy.

MS is a common disorder. Its prevalence ranges from 5 to 250 per 100,000,¹ with 250,000 to 350,000 MS patients in the US,² a similar number in Europe and a worldwide estimate of over 2,000,000 patients.^{3,4} It also carries a high commercial potential: it is estimated that the worldwide market for MS therapy is 2.5 billion US\$ annually,⁴ a fact that boosted many pharmaceutical companies to attempt to develop meaningful therapies.

Multiple sclerosis: Why do we understand so little and are unable to provide meaningful therapy?

Four immuno-modulating agents are widely used for relapsing remitting MS. Of these, three are forms of interferon (IFN)-beta [IFNbeta-1b (Bethaferon) and two preparations of IFNbeta-1a (Avonex and Rebif)], the fourth agent is a random polypeptide of four amino acids (glatiramer acetate, Copaxon). They are more or less equally distributed in the MS market with Avonex and glatiramer acetate leading the sales in the US and the three β -interferon agents equally promoted in Europe.

None, however, is the magic bullet for handling the disorder. A recent Cochrane review summarized all randomised, placebo-controlled trials of glatiramer acetate in MS concluding that: "Glatiramer acetate did not show any beneficial effect on the main outcome measures in MS, i.e. disease progression, and it does not substantially affect the risk of clinical relapses. Therefore its routine use in clinical practice is not currently supported".⁵ An earlier report relating to β -interferon was not much more enthusiastic: "The efficacy of interferon on exacerbations and disease progression in patients with relapsing remitting MS was modest after one and two years of treatment. It was not possible to conduct a quantitative analysis beyond two years."⁶

As for the many immuno suppressive agents, the Cochrane library is equally discouraging in relation to methotrexate and cyclophosphamide.^{7,8}

What are the reasons for this situation? We have tried before to list some of the causes for the stagnation in the field.⁹ The present review summarizes and updates the arguments presented before and attempts to offer our personal view that might contribute in promoting some novel approaches to the study of MS.

The meaninglessly broad spectrum of diagnostic criteria.

MS is defined as a chronic white matter disease of the central nervous system (CNS). The most widely used clinical scheme for the diagnosis of MS is still that of Schumacher et al., from 1965.¹⁰ It requires: (a) evidence for at least two episodes of (b) objective neurological deficit (c) resulting from white matter dysfunction, (d) localized to different sites within the CNS, (e) onset between 10 and 50 years of age. Lack of an alternative explanation is the sixth criterion that puts the entire diagnosis in the context of diagnosis by exclusion, and emphasizes the fact that there is still no biological marker with sensitivity and specificity to enable diagnosis. Thus, over the years, many individuals with disorders such as Behçet's disease, CNS vasculitis and mitochondrial encephalomyelitis were probably diagnosed and managed as MS, because at that time, they fit into the criteria. With time, these disorders were defined and excluded, but other, as yet indefinable, diseases are probably still grouped together with MS.

This set of coordinates provides a roof to host an extremely wide spectrum of clinical conditions. Patients who have two episodes of optic neuritis during 50 years without any other functional abnormality, young patients who become wheelchair-bound because of severe ataxia, completely paralyzed and immobile patients due to profound damage to the pyramidal system and patients who never seek the help of a physician since their disturbances are too minimal to bother (or they are unaware of them altogether) – all

receive the same diagnostic tag, are lumped into similar clinical trials and are subjected to the same therapies. The introduction of a new set of criteria by McDonald et al.,¹¹ intensified the problem, since they now enable the diagnosis in individuals with mono-symptomatic disorder and those with insidious chronic progressive abnormalities.

Apparently, even this vast clinical spectrum is not enough and seems to be insufficient. Pure gray matter involvement, up to overt dementia, epilepsy and 'well documented' cases in childhood and infancy, are all present in the literature.¹²⁻¹⁵

Beyond the risk of misdiagnosis and the unjustifiable subjection of patients to the disproportional grave implications of MS diagnosis, two highly important implications render these criteria deleterious to the study of MS: (i) Clinical research is based on very heterogeneous study groups and the biological noise associated with such diversity hampers the ability to identify etiopathogenetic factors, environmental or endogenous; (ii) Potentially important data may be overlooked. Even if patients with different natural history suffer indeed from a disease with similar cause and pathogenesis, there must be additional, not less, and maybe even more important factors that govern the course and outcome of the disease. However, under the current situation, these aspects are not addressed or studied.

The inability to define the efficacy of therapies

In conditions of unknown etiology and pathogenesis, therapeutic trials are means to examine hypotheses on possible causes and mechanisms of tissue damage. Reliable information on the natural course of the disease in untreated patients is a prerequisite to evaluate the effect of any therapy. However, under the current clinical criteria, the natural history of MS assumes an immensely wide range, making it practically impossible, to estimate the prognosis of untreated patients. This point is illustrated by analysis and comparison of the initial studies that examined the effect of interferons and glatiramer acetate on relapses in MS.

β -interferon 1b (Bethaferon) was reported to be effective in the treatment of relapsing-relapsing MS since it reduced the annual relapse rate compared to the annual relapse rate of placebo-treated patients.¹⁶⁻¹⁸ In the latter, it was 1.44 in the first year and 1.18, 0.92, 0.88 and 0.81 during the following years, whereas in the β -interferon treated patients the annual relapse rate was 0.96, 0.85, 0.66, 0.67, and 0.57 respectively.

The copolymer 1 (Copaxon) study examined, in addition to the annual relapse rate, the effect of the medication upon the Expanded Disability Status Scale (EDSS) in patients with relapsing relapsing MS.¹⁹ The natural course of the disease varied dramatically according to the disability: the two years relapse rate was 2.25 in control patients with EDSS between 2 and 4, and only 1.44 in patients with baseline EDSS of 0–2. The treated group had a 1-year relapse rate of 0.59 compared to 0.84 for placebo.

The β -interferon 1a (Avonex) measured several variables such as progression on the EDSS but also exacerbations.²⁰ Over 2 years, the annual relapse rate was 0.9 in the placebo-treated patients versus 0.61 in pa-

tients receiving once weekly an intramuscular injection of β -interferon 1a.

Thus: (1) The three studies were performed in the same country and recruited patients from an identical population pool, but still had very different annual relapse rates in the placebo-treated group. Copolymer 1 placebo patients fared better even than some of the interferon treatment group; (2) Enrolling MS patients into the placebo arms of clinical studies is beneficial as these patients show a decline in relapse rate which is much faster than in historical controls; (3) The annual relapse rate of MS depends on factors which, if ignored, render evaluation of these studies useless. In many MS patients, clinical progression to secondary progressive disease is concomitant with a reduced relapse rate,²¹ and therefore assessment of disability progression must be a second principle endpoint in these studies. Indeed, the β -interferon 1a study was designed with disability reduction as its end-point,²⁰ and it demonstrated a reduction in disability progression in 13% of the patients after 2 treatment years.

All three studies also report a very similar reduction (around 30%) in the relapse rate. The almost identical results of clinical trials using different agents, and their inability to go beyond the 33% line, raise the possibility that the entire observed benefit is only a placebo effect, and that the significant deviation from the true placebo effect might be the outcome of partial unblinding of patients by the side-effects. It was suggested that $35.5 \pm 2.2\%$ of patients affected by various conditions proved to react positively to placebos,²² and a study that examined placebo effects in MS came up with similar results.²³

The β -interferons carry side-effects and they, like glatiramer acetate are expensive, and cumbersome to administer. Indeed, The National Institute for Clinical Excellence in the United Kingdom issued in January 2002 a statement saying that: "On the balance of their clinical and cost effectiveness, neither beta interferon nor glatiramer acetate are recommended for the treatment of multiple sclerosis (MS) in the National Health System in England and Wales". This evaluation was only minimally revised on the follow up assessment of November 2003.

Since none of the currently available and recommended therapies in relapsing-remitting MS induces a meaningful decrease in annual relapse rate nor does it significantly slow disease progression, it also seems reasonable to conclude that basic research on these agents is unlikely to yield important insights into the mechanisms responsible for tissue damage in MS.

Lack of fulfillment of criteria for an autoimmune condition

The prevailing hypothesis is that tissue damage in MS is mediated via autoimmune mechanisms.^{24,25} However, although more than 18K publications with "Multiple sclerosis" in the title are listed in Pubmed up to 2005, and despite the fact that every immunological technique coming into fashion has been applied to the study of the disorder, MS fulfills none of the criteria of an autoimmune disease (see also ref. 26).

The criteria include: (i) identification of the autoantigen; (ii) the ability to induce in experimental animals

with such an antigen an autoimmune model mimicking clinically and pathologically the human condition; (iii) characterization of the immunological processes responsible for the disease; (iv) the ability to modify, arrest and treat the disorder, in the animal model and in humans with immunomodulating and immunosuppressive agents; and (v) the ability to passively transfer the condition from humans to experimental animals.

But: (i) the target antigen(s) in MS are unknown; (ii) there is no satisfactory immune-mediated animal model for MS (see below); (iii) the immunological mechanisms underlying MS, if any, are unknown.^{24,25} The abundant information gathered leads to conflicting results and their relevance to the human situation is questionable. Use of terms such as 'epitope spreading' or 'coordinated immunological attack against myelin' appear to suggest bewilderment rather than understanding. (iv) Intensive research, for almost four decades, has just confirmed the observation that an acute MS attack can be affected by intravenous corticosteroids.²⁷ The list of immunosuppressive and immunomodulating agents and therapies as well as treatment protocols, that have and are being used alone or in combinations to treat MS without significant effect is enormous.^{28,29} This is in striking contrast with other autoimmune diseases such as myasthenia gravis,³⁰ or conditions with a putative dysimmune pathogenesis such as polyarteritis nodosa.³¹ (v) There is only a single report of passive transfer of demyelination from MS patients.³² This could not be confirmed or reproduced.³³

EAE can be induced in laboratory animals by injection of spinal cord homogenates or purified myelin protein, and is characterized clinically by a monophasic nature, and histopathologically by T-cell infiltration and very little focal demyelination.³⁴ Moreover, the disease seems to be CD4 mediated (unlike the concept that MS is CD8-mediated). Indeed, many agents, therapies and immunomodulating protocols that prevent and/or arrest EAE, have no effect upon the course of MS. However, this model, first described in monkeys more than 70 years ago has governed MS research. While it enabled us to attain much information on basic general immunological mechanisms and dominated the discipline of neuroimmunology, it did not provide clues regarding possible immune-mediated mechanisms in MS.

There are other experimental animal models, derived from EAE, that have a more chronic relapsing course. None, however, helped to confirm the autoimmune nature of MS, nor did they pave the way to the development of therapies with significant short or long-lasting effect in MS.

The pressure from the biomedical industry

Several factors combine to prompt the biomedical industry to influence basic and clinical MS research:

- i. Being a fairly common disease, there is no doubt that a drug that promises to alter the natural course of MS will carry significant economical rewards.
- ii. The US Food and Drug Administration (FDA) has shortened the proceedings and reduced the requirements for approval of medications.³⁵ Mainly due to pressure from the AIDS and the cancer lobbies, it also affects the confirmation for therapeutic usage of drugs for other diseases. Moreover, an active and influential MS lobby with access to the media, presses to shorten the approval time for new medications

Multiple sclerosis: Why do we understand so little and are unable to provide meaningful therapy?

aimed to treat the disease.

iii. With decrease of federal and national funding budgets,^{36,37} the biomedical industry has become one of the leading sponsors and funders of medical, basic and clinical research.³⁸

All this results in the industry directing and pushing research within and outside academic institutions that is aimed at quick and easy gains. It is not unique to neurology or to MS, but it is felt in the arena of this disorder quite acutely. Neurologists and neuroscientists whose main objective should be the study of the etiology and pathogenesis of MS, when funded by the biomedical industry, are, not intentionally, active in the service of promotion of a specific compound. Moreover, at the clinical therapeutic level, the neurological medical establishment is currently under heavy pressure from the pharmaceutical companies trying to promote drugs for MS.³⁹ Since none promises cure, or a dramatic symptomatic improvement, their shelf-life will be relatively short. A new generation of medications may soon be available to replace the current ones.

Probable Solutions

Conclusions must follow from the present critique. Based on the problems outlined above, we can offer several guidelines, which we believe may shorten the path to elucidating the etiology and pathogenesis of MS, as means to provide cure to this disease.

I. Redefine the clinical criteria for diagnosis in order to group under the same heading patients with similar homogeneous disorders.

II. The new set of classification should be based on disease course. Annual number of attacks and the degree of disability, monitored for several years, will enable to distinguish between patients with benign, severe or malignant rate of CNS destruction.

III. Clinical studies should consist of patients who share the same clinical features, have an identical diagnosis, follow a similar disease course, and in whom all the known and identifiable variables are controlled. Clinical study groups for any question should be homogeneous.

IV. A uniform set of end points to evaluate clinical therapeutic trials should be agreed upon. This ought to include disease progression and evaluation of the cumulative functional disability as the major criteria, and will enable to measure, compare and judge the various clinical trials.

V. The autoimmune avenue has been extensively explored with discouraging results and has led MS research nowhere. While censorship and restrictions in science are deplorable, governments and national and private funding institutions can, should, and are setting priorities. A moratorium on the autoimmunity hypothesis in MS will enable to redirect funds for research with lower emphasis on autoimmunity, but rather on novel approaches to the problem. It will stimulate research in other directions and provoke fresh thinking and work which up to now were paralyzed by the autoimmunity dogma and establishment.

VI. A new set of ethical requirements, limiting the ability of the biomedical industry to influence, interfere

with, and/or dictate academic research, and publications should be agreed upon.

References

- (1) Pugliatti M, Sotgiu S, Rosati G. The worldwide prevalence of multiple sclerosis. *Clin Neurol Neurosurg* 2002;104:182-91.
- (2) Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol* 1992;31:333-336.
- (3) Rosati G. Descriptive epidemiology of multiple sclerosis in Europe in the 1980s: a critical overview. *Ann Neurol* 1994; 36(Suppl 2):S164-S174.
- (4) Khan O, Zabad R, Caon C, Zvartau-Hind M, Tselis A, Lisak R. Comparative assessment of immunomodulating therapies for relapsing-remitting multiple sclerosis. *CNS Drugs*. 2002;16(8):563-78.
- (5) Munari L, Lovati R, Boiko A. Therapy with glatiramer acetate for multiple sclerosis. *Cochrane Database Syst Rev*. 2004;(1):CD004678.
- (6) Rice GP, Incurvaia B, Munari L, et. al. Interferon in relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev*. 2001:CD002002.
- (7) Gray O, McDonnell GV, Forbes RB. Methotrexate for multiple sclerosis. *Cochrane Database Syst Rev*. 2004:CD003208.
- (8) La Mantia L, Milanese C, Mascoli N, Incurvaia B, D'Amico R, Weinstock-Guttman B. Cyclophosphamide for multiple sclerosis. *Cochrane Database Syst Rev*. 2002:CD002819.
- (9) Steiner I, Wirguin I. Multiple sclerosis--in need of a critical reappraisal. *Med Hypotheses*. 2000;54:99-106.
- (10) Schumacher G A, Beebe G, Kubler R F Et. al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann NY Acad Sci* 1965;122:522-568.
- (11) 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;50:121-7.
- (12) Zarei M, Chandran S, Compston A, Hodges J. Cognitive presentation of multiple sclerosis: evidence for a cortical variant. *J Neurol Neurosurg Psychiatry*. 2003;74:872-877.
- (13) Gambardella A, Valentino P, Labate A, et.al. Temporal lobe epilepsy as a unique manifestation of multiple sclerosis. *Can J Neurol Sci*. 2003;30:228-32.
- (14) Shaw C. M., Alvord E. C. Multiple sclerosis beginning in infancy. *J Child Neurol* 1987;2: 52-256.
- (15) Gadoth N. Multiple sclerosis in children. *Brain Dev*. 2003;25:229-32.
- (16) The IFNB Multiple Sclerosis Study Group. Interferon beta 1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double blind, placebo controlled trial. *Neurology* 1993; 43: 655-661.
- (17) Paty D W, Li D K B, the UBC MS/MRI Study group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized double-blind placebo-controlled trial. *Neurology* 1993; 43: 662-667.
- (18) The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis group. Interferon beta-1b in the treatment of

- multiple sclerosis: Final outcome of the randomized controlled trial. *Neurology* 1995; 45: 1277–1285.
- (19) Johnson K P, Brooks B R, Cohen J A, 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. *Neurology* 1995; 45: 1268–1276.
- (20) Jacobs L D, Cookfair D L, Rudick R A, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996;39:285–294.
- (21) Weinschenker B G, Sibley W A. Natural history and treatment of multiple sclerosis. *Curr Opin Neurol Neurosurg* 1992; 5: 203–211.
- (22) de Oliveira GG. The Placebo Effect: A Brief Review. *Am J Ther* 1995;2:217-224.
- (23) La Mantia L, Eoli M, Salmaggi A, Milanese C. Does a placebo-effect exist in clinical trials on multiple sclerosis? Review of the literature. *Ital J Neurol Sci* 1996;17:135-9.
- (24) Steinman L. Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. *Cell* 1996; 85: 299–302.
- (25) Hohlfeld R, Wekerle H. Autoimmune concepts of multiple sclerosis as a basis for selective immunotherapy: from pipe dreams to (therapeutic) pipelines. *Proc Natl Acad Sci U S A*. 2004;101(Suppl 2):14599-606.
- (26) Chaudhuri A, Behan PO. Multiple sclerosis is not an autoimmune disease. *Arch Neurol*. 2004;61:1610-2.
- (27) Filippini G, Brusaferrri F, Sibley WA, et. al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev*. 2000:CD001331.
- (28) Ebers G C. Treatment of multiple sclerosis. *Lancet* 1994; 343: 275–279.
- (29) Weiner HL. Immunosuppressive treatment in multiple sclerosis. *J Neurol Sci* 2004;223:1-11.
- (30) Lewis R. A., Selwa J. F., Lisak R. P. Myasthenia gravis: immunological mechanism and immunotherapy. *Ann Neurol* 1995; 37(S1): S51–S62.
- (31) Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. *Clinical Aspects and treatment*. *Rheum Dis Clin North Am* 1995; 21: 911–947.
- (32) Saeki Y, Mima T, Sakoda S, et al. Transfer of multiple sclerosis into severe combined immunodeficiency mice by mononuclear cells from cerebrospinal fluid of the patients. *Proc Natl Acad Sci USA* 1992; 89: 6157–6161.
- (33) Hao Q, Saida T, Nishimura M, Ozawa K, Saida K. Failure to transfer multiple sclerosis into severe combined immunodeficiency mice by mononuclear cells from CSF of patients. *Neurology* 1994; 44: 163–165.
- (34) Swanborg R. H. Experimental autoimmune encephalomyelitis in rodents as a model for human demyelinating disease. *Clin Immunol Immunopathol* 1995;77:4–13.
- (35) Kessler D. A., Feiden K. L. Faster evaluation of vital drugs. *Sci Am* 1995;272:26–33.
- (36) Mervis J. Clinton holds the line on R&D. *Science* 1995; 267: 780–782.
- (37) Arrow KJ, Axelrod J, Benacerraf B, et al. Nobel laureates' letter to President Bush. *Washington Post*. 2001 Feb 22:A02
- (38) Blumental D, Causino N, Campbell E, Seashore K. Relationship between academic institutions and industry in the life sciences – an industry survey. *N Engl J Med* 1996; 334: 368–373.
- (39) Daroff R. B. Editorials in scientific publications. *Neurology* 1966; 46: 883.

Reviewer 1

I think that these statements are exaggerated, but still some other thoughts in the text do add important ideas to present research, especially the analysis of the diagnostic criteria and the discussion about “half blinding” of the controlled studies. The headline is rather provocative, and first of all it is the task of the editor to estimate if it is in line with the goals of this journal. Of course, one could use this paper in dialogue or discussion IN the journal and invite a successful MS researcher to give his/hers points of view. In conclusion, I think that some important ideas in the paper motivate a publication, but the editor has to deal with the problem that it is extraordinarily political and rhetorical.

Anonymous

Reviewer 2

The paper has some problems; however, it would be interesting to invite ideas and comments by the researchers in this field through this thought provoking article. If the editors like, the manuscript may be published in the present form, subject to minor desk editing.

Anonymous

Reviewer 3

I like the ideas of the author, although a bit strange way of presentation and appears politically motivated and rhetorical. However, the paper has some important substance for the subject.

Anonymous