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Chaos theory for clinical manifestations in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a demyelinating disease which characteristically shows repeated relapses and remissions irregularly in the central nervous system. At present, the pathological mechanism of MS is unknown and we do not have any theories or mathematical models to explain its disseminated patterns in time and space. In this paper, we present a new theoretical model from a viewpoint of complex system with chaos model to reproduce and explain the non-linear clinical and pathological manifestations in MS. First, we adopted a discrete logistic equation with non-linear dynamics to prepare a scalar quantity for the strength of pathogenic factor at a specific location of the central nervous system at a specific time to reflect the negative feedback in immunity. Then, we set distinct minimum thresholds in the above-mentioned scalar quantity for demyelination possibly causing clinical relapses and for cerebral atrophy. With this simple model, we could theoretically reproduce all the subtypes of relapsing-remitting MS, primary progressive MS, and secondary progressive MS. With the sensitivity to initial conditions and sensitivity to minute change in parameters of the chaos theory, we could also reproduce the spatial dissemination. Such chaotic behavior could be reproduced with other similar upward-convex functions with appropriate set of initial conditions and parameters. In conclusion, by applying chaos theory to the three-dimensional scalar field of the central nervous system, we can reproduce the non-linear outcome of the clinical course and explain the unsolved disseminations in time and space of the MS patients.

Introduction

Autoimmune-related diseases are likely to have elevated immune activity and abnormal immune response, though whether they are primary or secondary are not necessarily clear [1]. Such abnormal immune strength is sometimes difficult to be measured with a single laboratory biomarker when the pathological mechanism is uncertain. In the complex system in immunity, many types of blood cells (*e.g.* lymphocytes) and tissue cells (*e.g.* microglia) play complex roles with mutual interactions. Large numbers of many other factors like cytokines, chemokines, and permeability of blood-brain barrier make the complex interactions even more complicated [2–6]. In addition to these numerous players of immune system, countless numbers of endogenous and exogenous factors (*e.g.* sex, age, race, food, stress, infection, vaccination, tobacco, medications, pregnancy, *etc.*) also affect the system [7–12].

At present, in the field of clinical neurology, one of the most mysterious autoimmune-related diseases with unknown causes is multiple sclerosis (MS). MS is a famous demyelinating disease in the central nervous system (CNS) with irregular clinical relapses and disseminated CNS lesions. The pathogenesis of MS is not fully known, but it has been suggested to be multifactorial (*e.g.* auto-immunity, diet, vitamin D, higher latitude, Epstein-Barr virus infection, and smoking) with possible causal cascades [13–16]. There are at least three subtypes as its clinical courses: primary-progressive MS (PPMS), relapsing-remitting MS (RRMS), and secondary-progressive MS (SPMS) transitioned from RRMS [17]. Characteristic conventional subtype of MS is RRMS, in which both of subclinical cerebral atrophy and clinical relapses take place with dissemination in time and space [18,19]. PPMS is also a worrisome phenotype; it shows almost no clinical relapses but shows faster cerebral atrophy than RRMS from an early stage [20–22]. Although tremendous amounts of researches have been conducted in MS, we are still on the way to identify its primary etiology and pathological mechanism.

In demyelinating diseases, several mathematical models have been proposed to explain the concentric pattern of demyelinating lesions, mainly focusing on the recruitment and activation levels of the macrophages [23,24]. With these conventional models, we can reproduce and explain the appearance of cerebral lesions in demyelinating diseases. As a next step, to explain the non-linear irregular clinical course

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and disseminated distribution of the lesions in MS, we need an additional disease model for MS.

To explain phenomena with such unpredictable patterns in time and space, one of the promising methods would be the complex system model with chaos theory [25]. Chaos theory has been widely applied in the field of meteorology, astronomy, and economics to explain the unpredictable non-linear actual phenomena in these fields. From before, it has been suggested that this mathematical model could be applied to the actual physiological phenomenon with oscillating patterns in the actual human body [26]. However, such considerations have been conducted in the field of hematologic diseases and we do not know whether we can apply such chaotic model even to neurological diseases like MS.

In this report, to invent a new theoretical model of MS to explain its irregular clinical characteristics (*i.e.* dissemination in time, dissemination in space, or accelerated cerebral atrophy), we considered the possible application of the model in MS and investigated whether we can develop a new disease model mainly based on chaotic model to comprehensively reproduce the clinical manifestations in MS.

Material and methods

Logistic map and discrete logistic equation of immune strength

There are tremendous amount of blood cells and cytokines that play roles in the immune system and we do not know which of the element plays the primary pathogenic role in MS. Thus, we cannot actually measure the strength of pathogenic immunological activity in MS in the clinical site yet. However, considering the characteristic clinical course and MRI patterns in MS patients, we can rationally suppose that the primary pathogenic factor or the decisive immune abnormality in each MS patient would be temporally homogeneous and could be theoretically expressed as a single scalar quantity at each point of location and time. Whether all MS patients are suffered from the same pathophysiology or not is uncertain; however, preparing a scalar quantity to express the strength of decisive pathogenic factor in each MS patient would not cause a theoretical contradiction.

Based on this premise, in this study, we suppose a scalar quantity of positive real number between 0.0 and $+\infty$ to express the pathogenic immune strength at a specific location of CNS in each MS patient at a specific point of time. Because there is no definite upper limit of immune strength in the actual human body, we need to convert and roll up the scalar quantity into a limited range to be utilized in a model with complex system. For such numerical conversion, one of the most popular methods is the logistic equation or the logarithmic transformation [27,28]. Because low levels of pathogenic immune strength can be ignored here, sigmoidal functions with logistic equation, rather than the logarithmic functions, would be more suitable here [29]. Thus, in this report, conversion with logistic equation was supposed in rolling up the scalar quantity into a limited range. In Fig. 1, a sigmoidal curve based on logistic equation is shown. Each scalar quantity of immune strength between 0.0 and $+\infty$ can be converted into one-to-one corresponding value between 0.0 and 1.0. In this report, we define the converted value of the pathogenic immune strength as "S_t", where "S" stands for strength of immunity and "t" stands for a specific time.

Pathogenic immune strength in a specific location at time "t" $\mapsto S_t$

$$0.0 < S_t < 1.0 \quad (1)$$

In the immune system, negative feedback system plays an important role in suppressing its overrun and controlling the overall strength [30–32]. If the strength of pathogenic immunity (S_t) is hyper-activated at some point of time, it will somehow suppress the strength. In each MS patient at a specific point of time, such suppressive pressure on S_t can be expressed as a single parameter of scalar quantity. One of the most famous and simple methods to express such chronological

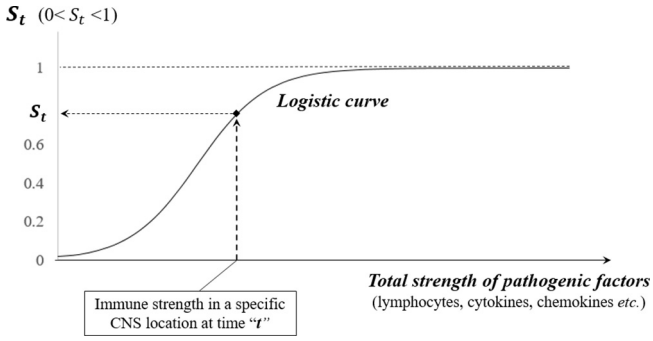

Fig. 1. Sigmoidal curve with logistic equation for numerical conversion. By using the logistic equation, pathogenic immune strength in MS will be converted into a scalar quantity (S_t) between 0.0 and 1.0. Abbreviations: MS, multiple sclerosis; S_t, pathogenic immune strength at the time of "t".

fluctuations with feedback system is the discrete logistic equation, also known as logistic map, as shown below [33,34].

$$x_{n+1} = a\ x_n(1-x_n) \quad (0.0 < a < 4.0) \quad (2)$$

In this equation, "x_n" is a variable and "a" is an arbitrary parameter between 0.0 and 4.0. This iterated function is most frequently used in a discussion of population change within limited space and resources, in which x_n stands for the population number of the n-th generation. Theoretically, this equation can also be applied to the pathogenic immune strength of S_t in MS, because such feedback system will require time periods with the orders of days to weeks to exert negative feedback in the living tissues, including the nervous system [35–37]. Here, we tentatively regard that $(t + 1)$-th cycle of the pathogenic immune strength (S_{t+1}) is regulated by that in t-th cycle with unknown period of the cycle. Then, a theoretical equation shown below can be derived.

$$S_{t+1} = a\ S_t(1-S_t) \quad (0.0 < a < 4.0) \quad (3)$$

In the right side of this discrete iterated function, S_t reflects the present strength of pathogenic immunity and $(1 - S_t)$ reflects negative feedback system that suppresses the excess immunity. Graph of this quadratic function, with S_t on X-axis and S_{t+1} on Y-axis, is shown on the left side of Fig. 2. In this figure, the space filled with grey color will be described in the next section. As shown in the right side of Fig. 2, vertex of the graph changes with different values of parameter "a". As the value of parameter "a" increases, the vertex will be vertically elevated and vice versa. Factors like infection, female, development of immune system in adolescence, and vaccinations would increase the value of parameter "a"; factors like senescence and immune-suppressants would decrease it.

Similar convex upward functions other than the equation [3] can also reproduce the feedback system of immunity, if the function and the parameter are appropriately prepared. An example of such function other than the Eq. (3) will be discussed and simulated in a later section ("Dissemination in space" section).

Model of cerebral atrophy and relapses in MS

In MS, subclinical accelerated cerebral atrophy is known to accompany even without apparent clinical relapses. A weak correlation between total number of relapses and grey matter volume is also suggested [21]. Based on these facts, we can estimate that there would be a common pathophysiology between the cerebral atrophy and clinical relapses in MS, though not identified yet. This concept is compatible with previous reports suggesting the responsibility of hyperactive immunity for the cerebral atrophy in MS patients [38]. Because there is a subgroup of patients who only present cerebral atrophy without apparent clinical relapses, known as PPMS, a threshold for the accelerated cerebral atrophy would be lower than that for clinical relapses.

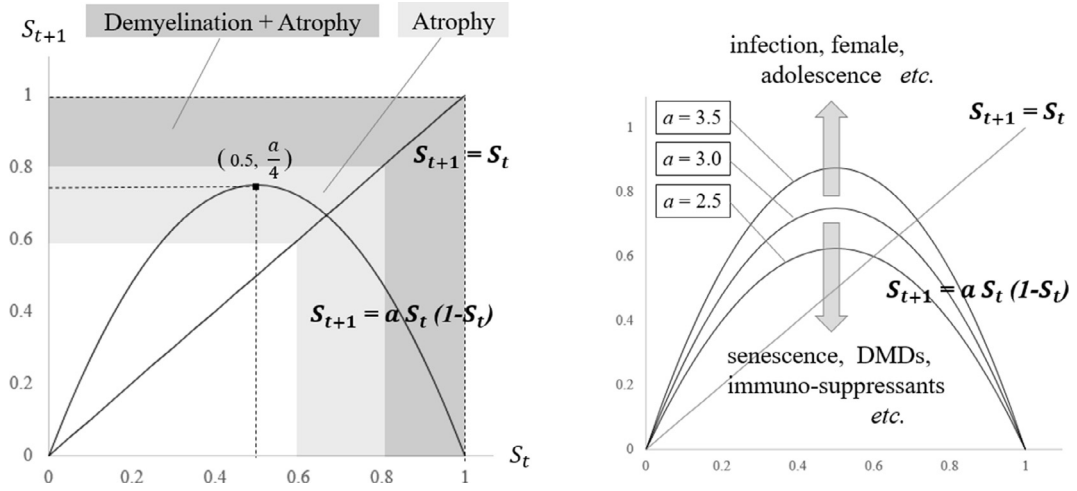

Fig. 2. Graph of the discrete logistic equation and effect of parameter "a". (Left) On the graph of discrete logistic equation, lower thresholds of S_t for an accelerated cerebral atrophy and clinical relapses are assumed. The parameters, pattern of the function, and the threshold lines could be different among the patients. (Right) Vertex of the discrete logistic function vertically moves as parameter "a" changes. Abbreviations: a, parameter "a" in Eq. (3), DMDs, disease modifying drugs; S_t, pathogenic immune strength at the time of "t".

Considering these bases together, we can set areas of S_t with an accelerated cerebral atrophy (filled with light grey) or clinical relapses (filled with dark grey) as shown in the left side of Fig. 2. Exact levels of these thresholds in S_t would widely vary among MS patients. In this figure, threshold of S_t for cerebral atrophy was tentatively set around 0.60 and that for clinical relapses was set around 0.80.

Cobweb plot and chronological fluctuation of immune strength

To investigate chronological behavioral pattern of S_t, which is regulated by the Eq. (3), we can use a method known as "cobweb plot", as shown in the left side of Fig. 3. By pursuing the track on this cobweb plot, eventual pattern of behavior (*e.g.* convergence, oscillation, chaotic *etc.*) can be visualized. In the right side of Fig. 3, an example of chronological behavioral pattern of S_t, with parameter a set at 2.0, is shown. In this case, as time passes and cycle number of t increases, S_t gradually converges toward 0.500. If parameter "a" and S_t are not changed by indirect causes, S_t will not part from 0.500, no matter how long we continue to observe. Also, if parameter "a" is constant, the behavioral pattern (convergence, oscillation, or chaotic) and the value of convergence will be the same, no matter of the setting of the initial value (S_0).

Dissemination in time and space of MS lesions

To discuss whether the complex system with chaos model is a good theory to explain and reproduce clinical manifestations in MS, we have to confirm that this model can reproduce all of the clinical subtypes, dissemination in time, and dissemination in space of MS lesions [18]. As to the reproduction of MS subtypes, we can judge by investigating analogy between chronological behavior of S_t and the characteristic clinical courses in each MS subtype. As to dissemination in time, we can simply judge by confirming that arbitrary upward-convex graphs of S_t and S_{t+1} can present chaotic behaviors. As to dissemination in space, we can judge by checking whether two adjacent location in CNS with very close initial value (S_0) and/or parameter "a" can produce completely different behavior of S_t with chaotic pattern.

Results

Relationship between the value of parameter "a" and relapses

The right side of Fig. 4 is the bifurcation diagram showing the distributional range of S_t for each value of the parameter "a", when the time period of "t" is enough large. As shown in the previous report, S_t converged to $(a-1)/a$ when parameter "a" is between 1.0 and 3.0.

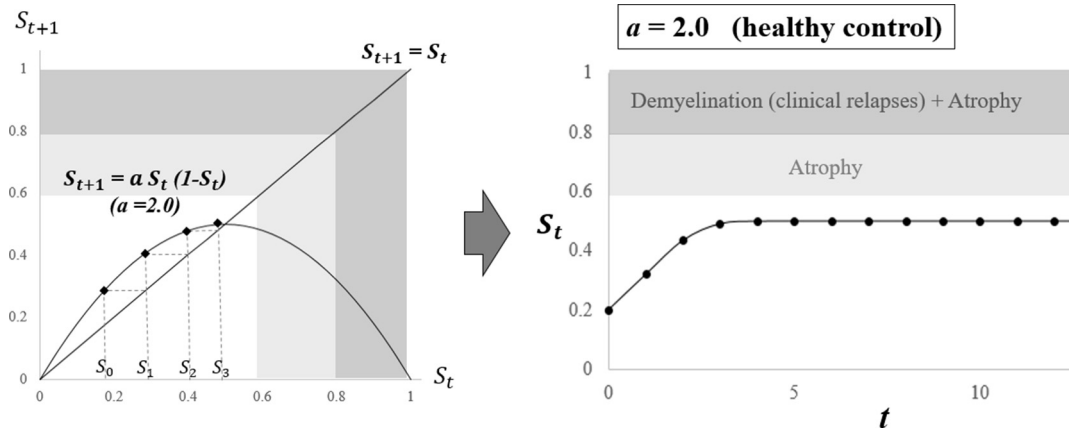

Fig. 3. An example of cobweb plot with parameter "a" set at 2.0. Discrete value of S_t gradually converges at 0.50 with parameter "a" fixed at 2.0. With the tentative settings of parameter "a" and threshold for cerebral atrophy in this figure, S_t will not reach an enough level to cause cerebral atrophy or relapses, no matter how long the time passes. Abbreviations: a, parameter "a" in Eq. (3); S_t, pathogenic immune strength at the time of "t"; S_0: initial condition of S_t; t, time.

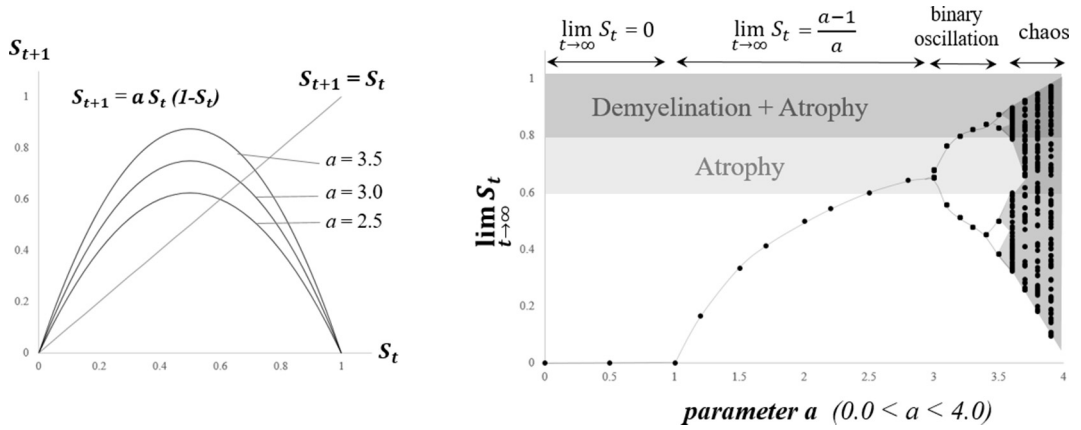

Fig. 4. Relationship of the behavioral pattern of S_t for each parameter "a" and the clinical episodes. S_t converges at one level when parameter "a" is between 0.0 and 3.0; S_t shows oscillating behavior between two levels when parameter a is between 3.0 and around 3.45; S_t shows chaotic behavior when parameter "a" is between 3.57 and 4.0. S_t with a higher value of parameter "a" is more likely to present both an accelerated cerebral atrophy and a chaotic behavioral pattern with irregular clinical relapses simultaneously. Abbreviations: a, parameter "a"; S_t, pathogenic immune strength at the time of "t".

When the value of "a" is between 3.57 and 4.0, it will show chaotic behavioral patterns [25].

Although the assumed threshold lines and the parameter "a" would be dramatically different among MS patients, it is almost certain that patients with the value of parameter "a" under which S_t surpass the threshold for clinical relapses will be more likely to show chaotic patterns in S_t.

Analogy of the chaos model with actual MS

Reproduction of each MS subtype and dissemination in time

Actual simulation of chronological behavior in S_t for each value of parameter "a" is shown in Fig. 5. Roughly speaking, behavioral patterns of S_t can be categorized into the following three types: convergence, oscillation, and chaotic.

As we can see in Fig. 5(b), even when S_t converges to a specific value, the convergence can take place above the threshold lines for cerebral atrophy and below the line for clinical relapses with a specific range of parameter "a". Such behavioral pattern may correspond to the clinical courses in PPMS and SPMS.

As parameter "a" becomes larger than a specific point, behavioral pattern of S_t come to show chaotic patterns, as shown in Fig. 5(d). This type of behavior could represent the conventional clinical course in RRMS. In this way, complex system with chaotic pattern can reproduce

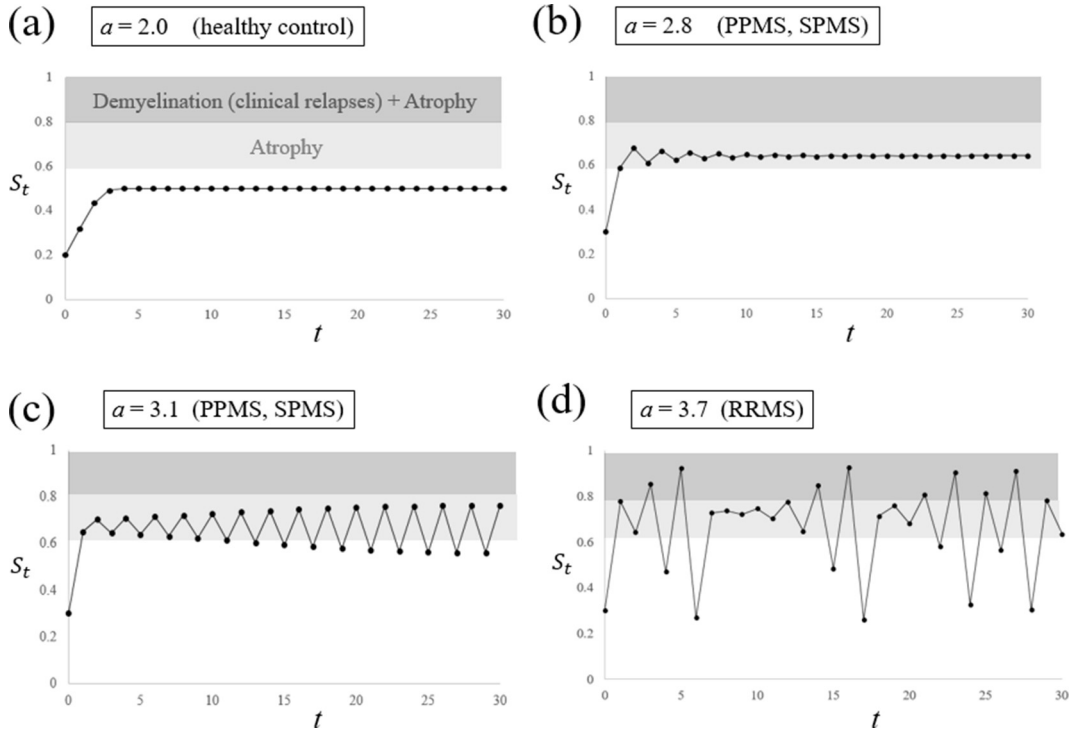

Fig. 5. Behavioral patterns of S_t and their analogies with MS subtypes. (a) S_t converges at one level below the threshold for cerebral atrophy, if the value of parameter "a" is small. (b) S_t converges at one level above the threshold for cerebral atrophy. This pattern could represent the progressive patterns in MS. (c) S_t shows oscillating pattern under parameter a within a specific range. (d) As parameter "a" becomes larger than a specific point around 3.57, S_t comes to show chaotic behavior and irregularly show values above the threshold for clinical relapses. Rate of cerebral atrophy would be slower than that in Fig. 5(b). This pattern could represent the conventional relapsing-remitting type. Abbreviations: a, parameter "a"; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; S_t, pathogenic immune strength at the time of "t"; t, time.

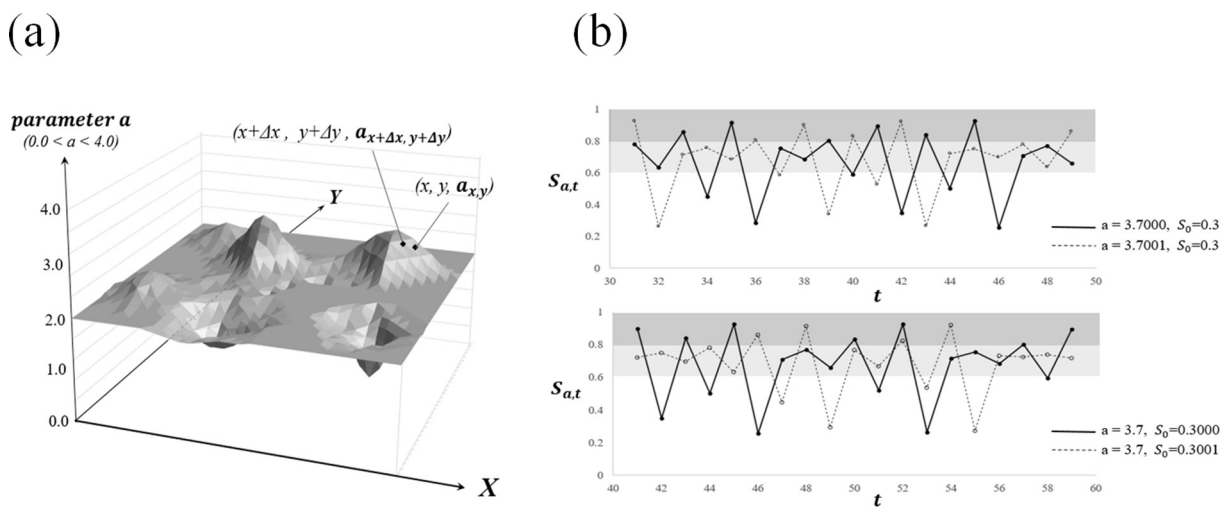

Fig. 6. (a) Geographical map of parameter "a" on the locational coordinates and (b) simulations showing chaotic behavior sensitive to minute differences in parameter "a" and initial condition (S_0). (a) In this virtual schema, location in central nervous system (CNS) is tentatively shown as two-dimensional plane for convenience with X-axis and Y-axis. At each location of (x, y), parameter "a" could take different values, which is shown as Z-axis. Value of parameter "a" at (x, y) and (x + Δx, y + Δy) would be almost similar, which are described as $a_{x,y}$and $a_{x+\Delta x,y+\Delta y}$in this figure, respectively. (b) Even minute changes in initial condition of S_t (S_0) and parameter "a" can produce dramatically different behavior of S_t after a sufficient period of time. These results of simulation could represent phenomena of "dissemination in time and space" in MS patients. Areas filled with light grey represents pathogenic immune strength causing accelerated cerebral atrophy; that with dark grey represents the strength causing clinical relapses. Abbreviations: a, parameter "a"; Δx, small increment of x; S_t, pathogenic immune strength at the time of "t"; $S_{a,t}$, S_t with a specific value of parameter "a"; S_0, initial condition of S_t; t, time.

all the MS subtypes.

In conclusion here, we can conclude that this model can reproduce the characteristic manifestation of dissemination in time.

Dissemination in space

To discuss about the reproducibility of "dissemination in space" with this model, we need to show that different two spots with very close distance in CNS can present dramatically different behavioral patterns in S_t. Otherwise, all MS lesions would be inevitably continuous, not disseminated, both in time and space; in such case, complex system cannot reproduce characteristic plaque lesions with clear margin in MS.

First, we will check whether a minute difference of parameter "a" between two adjacent spots in CNS can produce completely different chronological behavior of S_t or not. Fig. 6(a) depicts a virtual contour graph of parameter "a" as a scalar field on a tentative coordinate in the CNS. For convenience, in this geographical schema, coordinates in the CNS is expressed with two-dimensional shape (X and Y), though coordinates in the actual CNS tissue is ideally to be expressed as three-dimensional by using X, Y, and Z.

Because we can regard that parameter "a" would be continuous across a continuous space in the CNS, we can estimate that parameter "a" would be almost the same between two very close locations in CNS.

$$lim_{r\to 0}\ a_{(x+\Delta x,y+\Delta y)} = a_{(x,y)} \quad (r = \sqrt{\Delta x^2 + \Delta y^2}) \tag{4}$$

However, as shown in the upper side of Fig. 6(b), two distinct parameters of "a" and "$a + \Delta a$" with only a small difference (Δa) cannot produce similar or correlated chronological behaviors of S_t, if "t" becomes sufficiently large.

$$lim_{t\to\infty}(lim_{\Delta a\to 0}\ S_{(a+\Delta a),t}) \neq lim_{t\to\infty}\ S_{a,t} \quad (3.6599.\ ..\leq a < 4.0) \tag{5}$$

Next, we will check whether a minute difference of initial value (S_0) could produce a completely different chronological behavior of S_t or not. This is a phenomenon known as "sensitivity to initial conditions" of chaotic systems [39,40]. To make sure, we simulated whether a very small difference of initial values (S_0 = 0.3000 vs S_0 = 0.3001) could produce totally different behavioral patterns of S_t or not; and the resulted behavioral pattern was highly sensitive to the minute difference of initial condition, as shown in the lower side of Fig. 6(b).

At this point, we can conclude that the complex system with chaotic model can reproduce not only the "dissemination in time" but also the "dissemination in space" in MS.

Applicability of other similar non-linear functions for S_t

As we discussed in the material and methods section, Eq. (3) is only one of the possible recurrence relations of S_t that well reflect positive and negative feedback systems in immunity. To confirm that some different upward-convex functions may also produce chaotic behavioral patterns in S_t, a simple polygonal line function as shown below will be tentatively adopted, in which the symbol of || represents absolute value of the content.

$$S_{t+1} = a(1-|1-2\ S_t|) \quad (0.0 < a < 1.0) \tag{6}$$

The left side of Fig. 7 shows the graph of this Eq. (6). The right side of Fig. 7 shows the bifurcation diagram based on this function with parameter "a" on X-axis and distributional range of S_t after enough time period on Y-axis. As the same with Eq. (3), even a simple polygonal line function like Eq. (6) could also produce chaotic behavior of S_t, as shown in the right side of Fig. 7. In conclusion here, we confirmed that upward-convex functions other than Eq. (3), in which a specific value of S_{t+1} could be derived from two distinct values of S_t, may produce chaotic behavioral patterns in S_t, if parameter "a" is properly set.

Discussion

In this report, by using the complex system with chaotic model, we could satisfactorily reproduce the clinical subtypes of MS. And by taking concepts of "sensitivity to initial conditions" and "sensitivity to minute difference of the parameter" into account, we could also reproduce the clinical characteristics of "dissemination in time and space" in MS patients.

At the first point, we have to discuss whether we can apply a discrete function like Eq. (3) to actual immunological phenomenon in human body. Certainly, within a very short time period, feedback system of immune system could work as a kind of continuous function like the following differential equation, known as Hutchinson model [41,42].

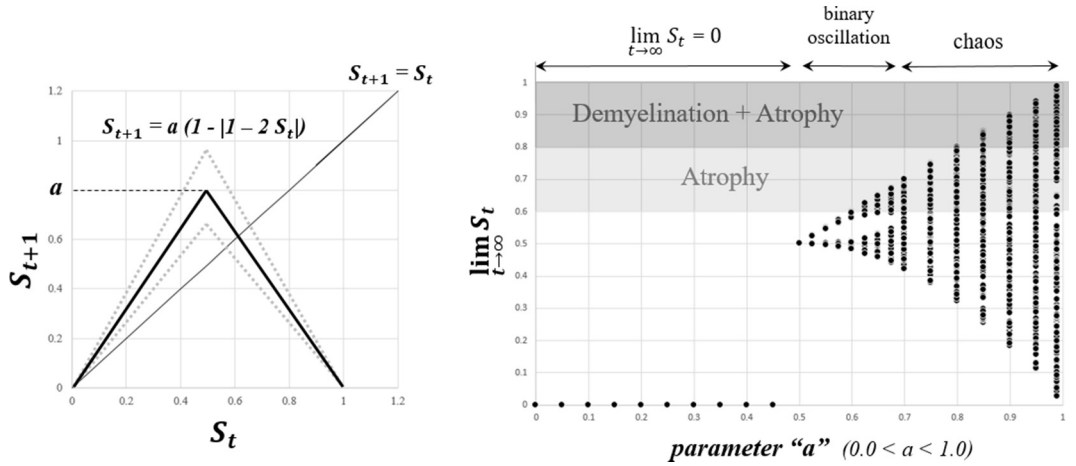

Fig. 7. Bifurcation diagram with a simple polygonal line function. An arbitrary upward-convex function like this simple shape could also produce a chaotic behavior in a specific range of the parameter "*a*". Abbreviation: S_t, pathogenic immune strength at the time of "*t*".

$$\frac{dS_t}{dt} = a\ S_t\left(1-\frac{S_{t-T}}{K}\right) \tag{7}$$

In this differential equation, "*a*" is a varying parameter specific to each individual, "*K*" is a constant value for each individual representing maximum capacity of immune system, and "*T*" stands for time delay of short span. Actually, with this model, we can also reproduce a permanent regular oscillation of S_t with appropriate settings of parameter "*a*", constant value of "*K*", and time delay of "*T*". However, in most settings of these variables, this equation brings a gradual convergence in S_t; thus, clinical manifestations cannot be reproduced with models based on Eq. (7). This equation may stand if the immune system is in fully stable condition and unaffected from any internal and external factors, in which situation the immune strength can be regarded as a continuous variable. But in actual human body, immune system is irregularly affected by numerous internal or external affectors, resulting in intermittent immune responses that would significantly shift the immune strength at each point of time. Such responses would require a time period in the scale of days or weeks, after which a new initial condition of S_0 and a slightly shifted value of parameter "*a*" would be given [36,43]. Based on these considerations, it would be more reasonable to assume a discrete logistic equation like (3) in considering the immune strength in living organisms. Certainly, we cannot reproduce the irregular complex pattern of the clinical course in MS only with a continuous model like the logistic equation; such model would surely result in a convergence to a specific level. We need a discrete function like the logistic map to reproduce such irregular complex model.

Characteristic pattern of clinical course in MS patients are the clinical onset in their late 20 s and the transition to SPMS with decreased relapses in their 40 s and 50 s [44,45]. This new model can also explain these characteristic clinical courses in MS. As described in the section "Reproduction of each MS subtype and dissemination in time", this new model can independently reproduce all subtypes of PPMS, RRMS, and SPMS, by appropriately setting the value of parameter "*a*". Now, the general strength of immune response in human body is thought to reach its peak in the early 20 s and gradually decrease up to the middle age [45–48]. This fact can be applied to the new model with a changed value of parameter "*a*" for the age-dependent strength of immune response. As the strength of immune response gradually increase with immune maturation, represented by the elevation of parameter "*a*", the value of S_t will more likely to show the chronological pattern as shown in Fig. 5(d). On the other hand, as the strength of immune response gradually decrease with immune-senescence, represented by the decrement of parameter "*a*", S_t will gradually come to show the patterns as shown in Fig. 5(b) or (c).

Lastly, we discuss about the different size and distribution of lesions not only among MS patients but also within each MS patient. Based on the presented new disease model for MS, the various size and shape of lesions in each MS patient can be explained by the specific size and shape of the distributed independent closed systems within each patient. The volume of each independent closed system in one patient would be regulated by multiple factors like the running of blood vessels, distance from the vessels, permeability of blood-brain barrier, or the lymphatic drainage system in the CNS [49,50]. These multiple factors for determining the size and distribution of each independent system in the CNS would produce the various size and shape of MS lesions in each patient. When we compare the chronological change of S_t in a closed system between different MS patients, not only the value of "*a*" but also the threshold levels would be totally different. Multiple factors mentioned in the introduction (*e.g.* geography, vitamin D, genetic background, Epstein-Barr virus infection, and smoking) would contribute to such interpersonal diversity.

Although this model can explain and reproduce many characteristics in MS, there are some limitations for this report. Unfortunately, at present, we have not known which of the immunological factors in MS patients correspond to the variable of S_t. Certainly, the elements that comprise a scalar quantity of S_t would not be single. By now, there have already been many immunological elements that are suggested to play important roles in the pathomechanism of MS, like B cells, Th17 cells, Th1/Th2 balance, and many others [51–54]. Though we do not know which of these candidates are more important than the others, we have some clues to estimate the important pathogenic affectors in MS. For example, in MS, an established treatment in the acute phase of relapses is high-dose intravenous prednisolone and those in the intermittent period as preventive therapies are interferon-β injection or oral fingolimod [54–56]. Based on these facts, we can infer that the provisional variable of S_t in this report would represent a fraction of immune system that is affected by these medications. Another limitation is that whether we can assume a single scalar quantity of S_t to represent the total sum of pathogenic immune strength in MS patients. Realistically, integrating multiple candidates at each moment into a single scalar quantity of S_t might be a little bit too radical. Even in that case, we can further apply couples of chaotic systems like coupled map lattice (CML) and globally coupled map (GCM) [57,58], and we shall have similar conclusions with this report. Or, maybe, we can simply redefine the pathogenic immune strength with a vector value and apply this chaotic model to each element of the vector. The last limitation of this study is that we do not know the exact values of parameters and the thresholds for brain atrophy and clinical relapses in each person, yet. At present, unfortunately, this model can be used only to explain the possible pathological mechanism in MS and it would not be useful as a diagnostic

or predictive model for MS patients.

Conclusions

In this report, a new theoretical disease model for MS based on complex system with chaos theory in the immune system has been introduced to explain the non-linear irregular pattern of clinical manifestations in MS. With this new disease model, we would be able to achieve new insights into the mysterious pathomechanism of MS.

Author contributions

TA contributed to study conception, simulation and interpretation of data, and drafting of manuscript.

TT contributed to study conception, interpretation of data, and critical revision to the manuscript.

IN contributed to interpretation of data, critical revision to the manuscript, and supervision of this study.

Conflict of interest

Tetsuya Akaishi – Reports no conflict of interest.

Toshiyuki Takahashi – Reports no conflict of interest.

Ichiro Nakashima – Received Funding for a Trip and Speaks from Biogen Japan, Mitsubishi Tanabe Pharma, Novartis Pharma, Takeda Pharmaceutical Company. Served as an editorial board member of Multiple Sclerosis International. Received grant support from LSI Medience Corporation.

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