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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

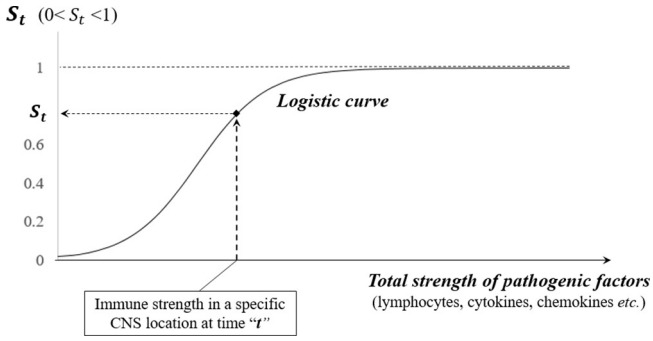

Fig. 1. Sigmoidal curve with logistic equation for numerical conversion. By using the logistic equation, pathogenic immune strength in MS will be converted into a scalar quantity (S_t) between 0.0 and 1.0. Abbreviations: MS, multiple sclerosis; S_t, pathogenic immune strength at the time of "t".

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.