Amino Acids (2001) 20: 155–162

Amino
Acids

Analysis of the disease course of HIV-1 by entropic chaos degree

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Accepted July 7, 2000

Summary. When a V3 sequence obtained on the n-th year after infection with human immunodeficiency virus type 1 (HIV-1) was supposed to change into a V3 sequence on the n + 1-th year, the variation between the above two sequences was analyzed by means of entropic chaos degree. The entropic chaos degree measures chaotic aspects of the dynamics causing the variation of sequence. If it is large, then the dynamics produces the large complexity, in other words, the variation of sequences becomes large.

As a result, the chaos degree for the dynamics changing the V3 region showed the specific variation patterns throughout from the early stages of infection to death. That is, the variation patterns indicated that the entropic chaos degree is useful to measure the stage of disease progression after HIV-1 infection.

Keywords: Amino acids – HIV-1 – Entropic chaos degree

1 Introduction

There exist several different quantities to measure chaotic aspects of dynamical systems. A new measure, entropic chaos degree, was successfully applied to several dynamics (Ohya, 1998). Therefore, we analyzed the variation of human immunodeficiency virus by using this new measure.

The third variable region (V3) contained in gp 120 is the principal neutralization determinant (Javaherian et al., 1989) and a epitope to recognize the cytotoxic T cell (Takahashi et al., 1999). Moreover it is known that the V3 region has a high substitution rate.

We calculated the entropic chaos degree of the dynamics leading from the variation of the V3 region which were observed from 19 patients infected with HIV-1 at several points in time after infection or seroconversion. Since the entropic chaos degree describes the stage of the variation, it can be considered that the state of the disease progression is characterized by this degree.

2 Materials and methods

2.1 Patient characteristics

The data of patients selected for this study were approximately taken once each year after HIV-infection or seroconversion (maximum; follow-up of 12 years, minimum; follow-up of 2 years). We used the sequences of the V3 region for virus clones in plasma, serum and peripheral blood mononuclear cells stored in the international DNA databases (DDBJ/EMBL/Genbank).

From nineteen HIV-infected patients, six patients (A, B, C, D, E and F) had progressed to AIDS and died of AIDS-related complications during the period of follow-up. Three patients (G, H and I) were diagnosed as having AIDS and were still alive during the period of follow-up. The remaining patients were asymptomatic throughout the period of follow-up (Table 1).

We will explain information of patients in detail. Patient A and B were infected with HIV-1 around 1983 (Ida et al., 1997). Patient A had progressed to AIDS by about 6 years after infection and died in 1992. Patient B had progressed to AIDS by about 7 years after infection and died in 1996. Patient C who seroconverted in 12/1985 had progressed to AIDS in 6/1990 (4.5 years after seroconversion) and died in 9/1993 (van't Wout et al., 1998a). Patient D, whose seroconverion day is not known, died 40 months after AIDS diagnosis (van't Wout et al., 1998a). Patient E who seroconverted in 1984 had progressed to AIDS in 4/1988 and died in 12/1991 (Cleland et al., 1996; Leigh Brown and Cleland,

Table 1. Patient characteristic

Patient	Duration of asymptomatic	Tissue	Duration of AIDS
Group 1			
A (tk-2)	about 6 years	PBMCs	about 3 years
B (tk-29)	about 7 years	PBMCs	about 6 years
C (ACH0208)	54 months	PBMCs	39 months
D (ACH6052)		PBMCs	40 months
E (p74)	about 4 years	PBMCs	44 months
F (p87)		PBMCs	>3 years
Group 2			
G (p495)	55 months	serum	
H (p39)	37 months	PBMCs	
I (p82)	7 years	plasma	
Group 3			
J (p1)	59 months	serum	
K (s5)	3 years	PBMCs	
L (s6)	4 years	PBMCs	
M (s7)	2 years	PBMCs	
N (s8)	3 years	PBMCs	
O (s9)	4 years	PBMCs	
P (s14)	4 years	PBMCs	
Q (q23)	about 2 years	cervival secretion	
R (tk-3)	about 12 years	PBMCs	
S (tk-22)	about 12 years	PBMCs	

(): designation in original paper; *PBMCs*: peripheral blood mononuclear cells.

Group 1: Patients died of AIDS-related complication, Group 2: Patients progressed to AIDS, Group 3: Patients maintained CD4+ T cell numbers above 200 for follow-up period.

Duration of asymptomatic in group 3 shows period until loss of follow-up.

1996). Patient F seroconverted in 1984, whose the time of AIDS diagnosis is not known, died in 9/1990 (Leigh Brown and Cleland, 1996).

Patient G was diagnosed as having AIDS in 1989; 55 months after primary infection (Wolfs et al., 1991). Patient H who seroconverted in 10/1987 progressed to AIDS in 11/1990 (van't Wout et al., 1998b). The $CD4^+$ T cell number of patient I decreased below 200 at 7 th year (Holmes et al., 1992).

Patient J remained healthy for 59 months after infection (Wolfs et al., 1991). Six patients' (K, L, M, N, O and P) $CD4^+$ T cell numbers have not been a level of fewer than 200 for 2–4 years from seroconversion until loss of follow-up Markham et al., 1998. Patient Q was not showing any symptoms of disease referable to HIV-1 for 2 years from seroconversion until loss of follow-up (Poss et al., 1998). Patient R and S were infected around 1983, who maintained stable $CD4^+$ T cell number until loss of follow-up (1995) (Ida et al., 1997).

2.2 Entropic chaos degree

When the sequences change year by year, that change can be estimated by entropic chaos degree. The entropic chaos degree for the sequence $X^{(n)}$ obtained on the n-th year after HIV-1 infection and that $X^{(n+1)}$ obtained on the $n + 1$-th year is given as follows: Two aligned amino acid sequences $X^{(n)}$ and $X^{(n+1)}$ composes of 20 kinds of amino acids and the gap after their alignment. The complete event system of $X^{(n)}$ is determined by the occurrence probability p_i of each amino acid a_i and p_0 of the gap (Sato et al., 1998);

$$\left(X^{(n)}, p^{(n)}\right) = \begin{pmatrix} * & a_1 & \cdots & a_{20} \\ p_0^{(n)} & p_1^{(n)} & \cdots & p_{20}^{(n)} \end{pmatrix}$$

In the same way, the complete event system of the $n + 1$-the year is;

$$\left(X^{(n+1)}, p^{(n+1)}\right) = \begin{pmatrix} * & a_1 & \cdots & a_{20} \\ p_0^{(n+1)} & p_1^{(n+1)} & \cdots & p_{20}^{(n+1)} \end{pmatrix}$$

The compound event system of $X^{(n)}$ and $X^{(n+1)}$ is denoted by

$$\left(X^{(n)} \times X^{(n+1)}, p^{(n,n+1)}\right) = \begin{pmatrix} ** & *a_1 & \cdots & a_{20}a_{20} \\ r_{00}^{(n,n+1)} & r_{01}^{(n,n+1)} & \cdots & r_{2020}^{(n,n+1)} \end{pmatrix}$$

$$\left(r^{(n,n+1)} = \left\{r_{ij}^{(n,n+1)}\right\}_{i=0,j=0}^{20,20}\right),$$

where r_{ij} represents the joint probability for the event i of the n-th year sequence and the event j of the $n + 1$-th year sequence.

We suppose the dynamics describing the change of sequence $X^{(n)}$ to $X^{(n+1)}$ is given by a certain mapping Λ called a channel for $p^{(n)}$ to $p^{(n+1)}$. It's very difficult to know the exact form of this mapping in the course of the variation of HIV-1. However, our entropic chaos degree can be used to measure the complexity without knowing the exact form (Ohya, 1998; Inoue et al., 2000).

The entropic chaos degree for the sequence obtained on the n-th year after HIV-1 infection and that on the $n + 1$-th year is given the following formula;

$$D_{\Lambda}^{(n)}(X) = \sum_{i,j} r_{ij}^{(n,n+1)} \log \frac{p_i^{(n)}}{r_{ij}^{(n,n+1)}}$$

Practically, we used the V3 sequences for some virus clones at each point in time. Therefore, we take the average of the entropic chaos degree, each of which is given as above. Note that for two dynamics Λ_1, Λ_2, $D(\Lambda_1) > D(\Lambda_2)$ if and only if Λ_1 produces larger change to a system than Λ_2.

3 Results

Figure 1 shows the change of the entropic chaos degree of V3 sequences obtained at several points in time during the clinical course of each patient. The value of the entropic chaos degree was low at the early stages of infection. However, from the time of primary infection until the time of AIDS diagnosis, the entropic chaos degree increased gradually and reached a maximum just after the time of AIDS diagnosis. Then, the chaos degree continued to decrease up to death for the duration of AIDS. Our study patients were classified into three groups; 1) patients who died of AIDS-related complications, 2) patients who progressed to AIDS, 3) asymptomatic patients who did not progress to AIDS during the period of follow-up. The values of the entropic chaos degree were higher in AIDS patients than in asymptomatic patients, as was shown in Fig. 2. For all patients of the group 1, the value of the entropic chaos degree had temporarily larger than 0.2. On the other hand, almost all patients of the group 3 showed the value below 0.15 over the period of study (5 of 10 patients; entropic chaos degree < 0.1, 4 of 10; < 0.15).

4 Discussion

We analyzed the variation of the V3 sequence by using the entropic chaos degree. This degree measures chaotic aspects of the dynamics causing the variation of sequence.

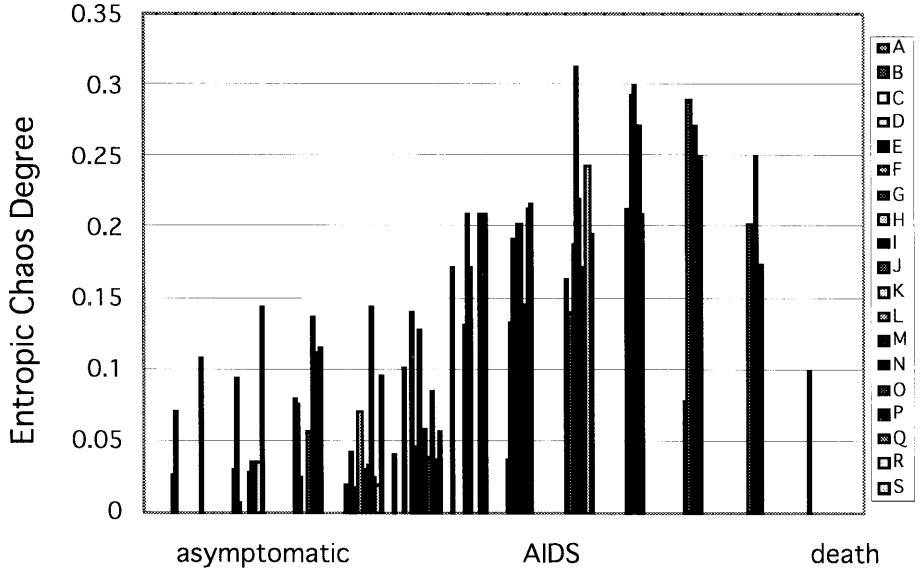

Fig. 1. The entropic chaos degree for V3 sequences obtained at several points in time of each patient are plotted altogether

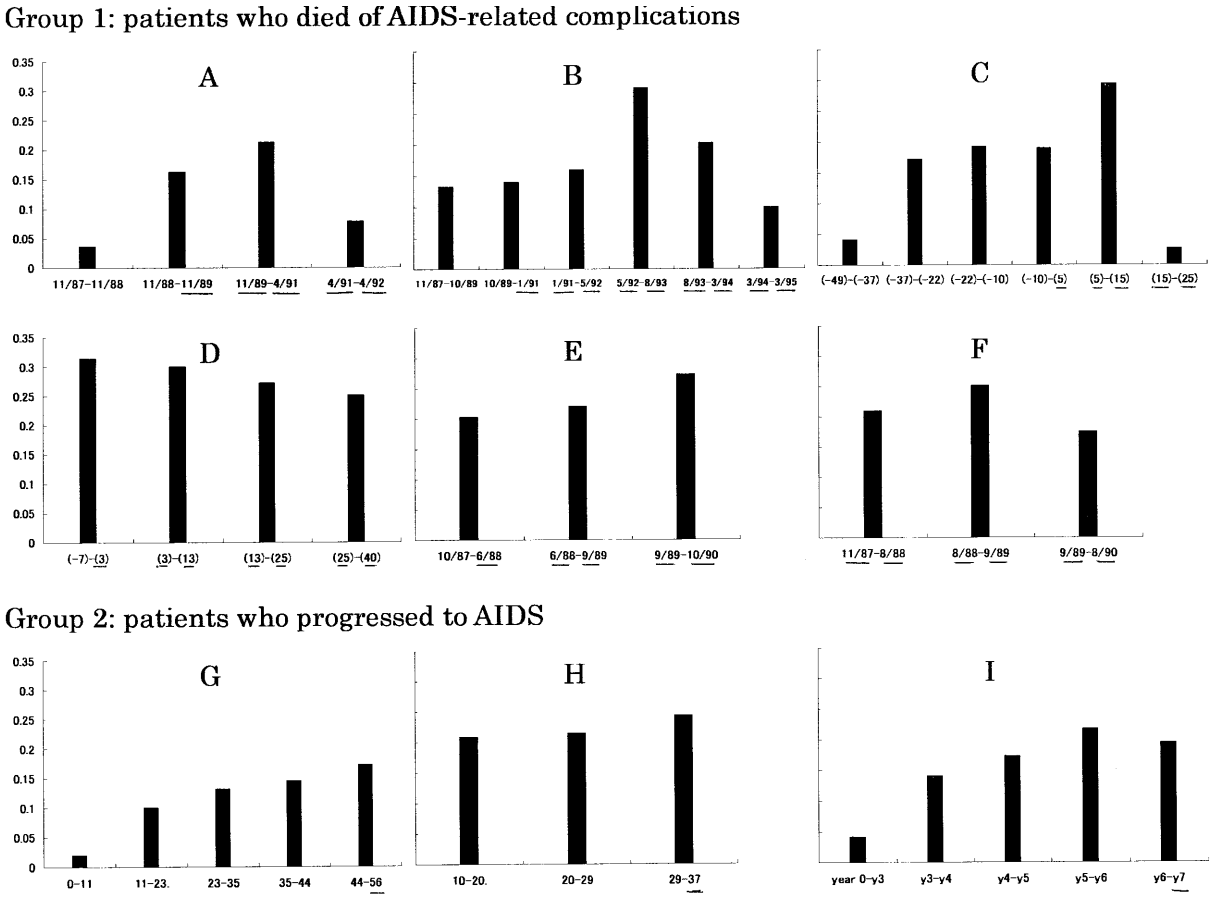

Fig. 2. Entropic chaos degree increased in group 1 and group 2 as AIDS developed, however remained low in group 3 except patient N. The time to be diagnosed as AIDS in indicated by underline

Whether patient progressed to AIDS or not is so far decided on depletion of $CD4^+$ T cell. Although the majority of patients infected with HIV-1 are considered to progress to AIDS, a small number of patients remain healthy and maintain $CD4^+$ T cell numbers or above 200 for more than a decade after infection. In addition to $CD4^+$ T cell, it is known that HIV-1 RNA level in plasma is closely related to the stage of the disease. However, it is hard to predict not only the time of the progress to AIDS and death relative to AIDS, but also rapid progressors or slow progressors.

From our results, patients who developed AIDS took the entropic chaos degree high value compared with patients who remain asymptomatic. All patients who died of AIDS-related complications surely took the value 0.2 or more during the period of study and died within 3–4 years thereafter. In contrast, patients who continued taking the value less than 0.1 or immediately going back to the value less than 0.1, even if the value transiently becomes larger than 0.1, were asymptomatic without AIDS. Our results indicate that the chaos degree increases with leading to AIDS after infection and attains

Group 3: patients who did not progressed to AIDS

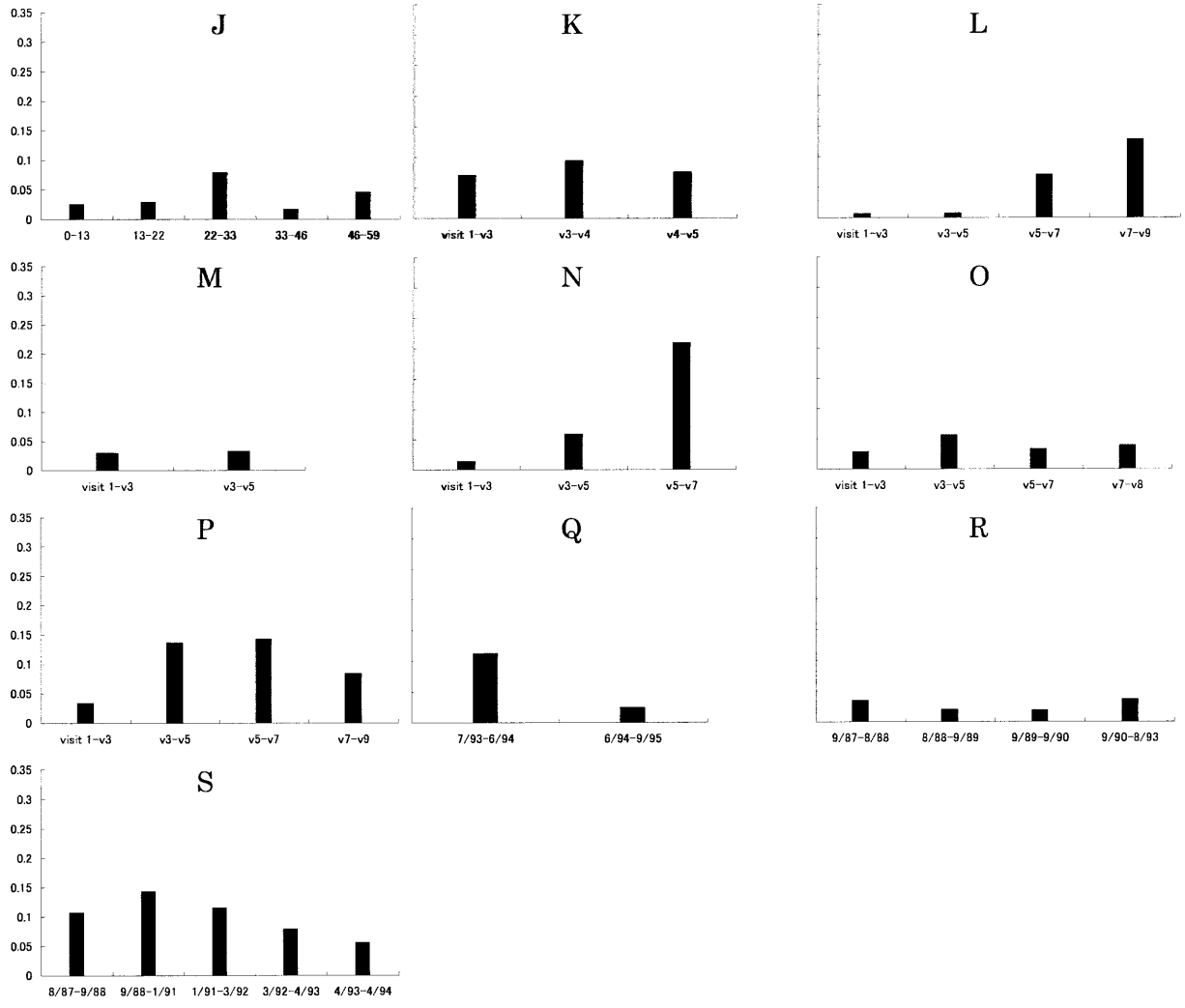

Fig. 2. *Continued*

the value larger than 0.2. Therefore, when the chaos degree has decreased after this increase without attaing high value like patient P and S or it has maintained stable and low value (<0.1) like patient J, K, M, O and R, those patients can be classified as long term non progressors. Patient N who appears to have been slow progressor was exceedingly close to AIDS development, because the value of the entropic chaos degree between 2 and 3 years (visit 5 and v 7) after seroconversion indicated larger value than 0.2 and drew a characteristic increase pattern such as AIDS patients.

Many researchers are exploring every makers to recongize AIDS development and disease progression, and there have been some diagnosis markers used to estimate prognosis in patients with HIV-1 infection (Mellors et al., 1995; Connor et al., 1996). We examined whether the entropic chaos

degree can be a candidate for these markers. Although the data used here are not sufficiently many so far, we in this paper propose that the entropic chaos degree can be one of the markers to estimate disease progression in HIV-1.

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Received April 1, 2000