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Mathematical Analysis of EEG of Patients with Non-fatal Nonspecific Diffuse Encephalitis

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***Abstract*—**Diffuse viral encephalitis may lack fever and other cardinal signs of infection and hence its distinction from other acute encephalopathic illnesses is challenging. Often, the EEG changes seen routinely are nonspecific and reflect diffuse encephalopathic changes only. The aim of this study was to use nonlinear dynamic mathematical techniques for analyzing the EEG data in order to look for any characteristic diagnostic patterns in diffuse forms of encephalitis.

It was diagnosed on clinical, imaging and cerebrospinal fluid criteria in three young male patients. Metabolic and toxic encephalopathies were ruled out through appropriate investigations. Digital EEGs were done on the 3rd to 5th day of onset. The digital EEGs of 5 male and 5 female age and sex matched healthy volunteers served as controls.

Two sample t-test indicated that there was no statistically significant difference between the average values in amplitude between the two groups. However, the standard deviation (or variance) of the EEG signals at FP1-F7 and FP2-F8 are significantly higher for the patients than the normal subjects. The regularisation dimension is significantly less for the patients (average between 1.24-1.43) when compared to the normal persons (average between 1.41-1.63) for the EEG signals from all locations except for the Fz-Cz signal. Similarly the wavelet dimension is significantly less (P = 0.05*) for the patients (1.122) when compared to the normal person (1.458). EEGs are subdued in the case of the patients with presence of uniform patterns, manifested in the values of regularisation and wavelet dimensions, when compared to the normal person, indicating a decrease in chaotic nature.

***Keywords*—**Chaos, Diffuse encephalitis, Electroencephalogram, Fractal dimension, Fourier spectrum.

I. INTRODUCTION

ENCEPHALITIS is an inflammation of the brain due to a variety of agents but mostly by virus [1]. It is a disease with very high mortality and morbidity. Early diagnosis and appropriate treatment may reduce deaths and devastating residual neurological sequelae from encephalitis [2], [3]. The Electroencephalaogram is an important diagnostic tool in encephalitis [4], [5]. Diffuse forms of encephalitis is characterized by generalized background slowing and epileptiform discharges, whereas focal encephalitis has more localized EEG changes such as focal slowing of background, focal epileptiform discharges, periodic lateralized epileptiform discharges (PLEDS) etc [6], [7]. In diffuse encephalitis, often, the EEG changes seen are nonspecific and reflect diffuse encephalopathic changes only. Diffuse viral encephalitis may lack fever and other cardinal signs of infection and hence its distinction from other acute encephalopathic illnesses is challenging [8], [9].

In this paper several nonlinear dynamic mathematical techniques are used to analyse the EEG data from diffuse encephalopathic patients and compared with normal subjects to understand the differences between the two wave forms and to bring out the underlying features. These techniques could be used as a tool for diagnosing such a disease form, since it is very difficult for general medical practitioner to identify the disease from the raw EEG data.

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II. MATERIALS AND METHODS

A. Patients' Data

Three patients were studied, all young males between 22-25 years age, admitted during the period July-August 2006 at the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, South India. All three had acute onset of headache, irregular fever, vomiting and altered sensorium with bilateral pyramidal signs and mild neck stiffness lasting for 5-7 days followed by gradual improvement. There were no preceding exanthematous fevers, vaccinations, animal bites or exposure to toxins or drugs. No past history of similar episodes, history of systemic diseases like diabetes, renal or liver disease or auto-immune diseases was known. There was no history suggestive of tuberculosis in the past or in the family members. As their acute state and sensorium started improving, all the three were in a wake and vigil state but continued to be non-communicative and in urinary retension. CT and MR scans of the brain on 2nd and 3rd days showed mild diffuse brain edema with no meningeal enhancement or exudates. Cerebrospinal fluid studies showed 10-15 lymphocytes per cumm, normal sugar, 45-55 mg% protein and normal chloride. The viral serology titres were studied and found to be insignificant for Herpes, HIV, HBsAg, Measles, Rabies and Japanese encephalitis. Paul Bunnel test for Ebstein-Barr virus was also negative. Serum cryptococcal, cysticercus,

leptospira, VDRL, Weil Felix and Widal tests were negative. Peripheral smear for parasites were negative as was the QBC for malaria. Metabolic profile including blood sugar values, urea and creatinine, serum electrolytes, serum ammonia and bilirubin, calcium and phosphorus and Serum alkaline phosphatase, and blood gases were within the normal limits. The Thyroid function tests were normal as well. Toxic screening for organophosphorus, hydrocarbons and heavy metals were also negative. There were no clinical features to suggest any nutritional encephalopathy. Thus the important and common non-infectious and infectious causes for coma were ruled out. Based on the clinical profile and CSF findings, non-specific diffuse type viral encephalitis was the final diagnosis. All the patients recovered without significant neurological sequelae by the second month.

EEG studies: Digital Video-EEG studies were performed in all the three patients during the 5th to 8th days of their illness without using any sedative in the wake stage for about 30 minutes. The universal 10-20 scalp surface Electrode placement system was followed. A 16 channel recording was done at the sensitivity of 7 microvolts per mm, with 1 Hz and 70 Hz as upper and lower frequency limits with a 50 Hz filter, at 10 seconds per page sweepspeed, using a Bravo (Nicolet, Vyasys) EEG system. Photic stimulation was done as a provocative measure in all the cases. Commands for hyperventilation were delivered to patients routinely and timing documented. Any spontaneous sleep during the study period was unintervened.

EEG studies were done similarly in five male and five normal adults whose average ages matched that of the patients for each gender, as controls with the same settings as above [10], [11].

B. Quantitative Mathematical Analysis of the Digital EEG

Several nonlinear dynamic mathematical techniques have been used for analyzing EEG data, in order to extract the hidden features, minimize noise and understand the spatio-temporal nature of the oscillations. These techniques help in differentiating the EEG signals of the diseased patients with the normal ones. Generally Epileptic EEG signals have been analysed using correlation dimension [12]. Theory of chaos has been applied to control seizure attacks. Fourier transform has been used to analysis sleep stages [13].

Several mathematical techniques are used in this paper for analysing the EEG signals which are normally used in analysing spatio-temporal signals. The following paragraphs describe these techniques such as t-test, ANOVA, Regularisation dimension, and Wavelet dimension and Appendix I gives the corresponding mathematical relations.

A times series or signal is a finite sequence of real values recorded over time in a space. This signal is transformed (using a specific transformation function) into a signal in a transformed space. To achieve dimensionality reduction some subset of the transformed coefficients are selected as features. These features form a feature space which is simply a projection of the transformed space. The Fourier transform is based on the observation that every signal can be represented by a superposition of sine and cosine waves.

Wavelet transforms give gradually refined representation of the signal of different scales, which correspond to basis functions of different length. The continuous wavelet transform (CWT) is a time–frequency analysis method which differs from the Fourier transform by allowing arbitrarily high localization in time of high frequency signal features. The CWT does this by having a variable window width, which is related to the scale of observation—a flexibility that allows for the isolation of the high frequency features. Another important distinction is that it is not limited to using sinusoidal analysing functions, but a large selection of localised waveforms can be employed as long as they satisfy predefined mathematical criteria.

Hausdorff dimension is the fundamental definition of the fractal dimension in the theory of fractal geometry. It is difficult to measure the dimension of a set directly from the definition. Many alternative methods of measuring the dimension of a set have been developed. Regularisation dimension has been proposed as an approximate to the Hausdorff dimension. The advantages of the regularisation dimension are: i) it is more precise than other approximation methods; ii) it is easy to derive an estimator in the presence of noise due to the fully analytical definition [15]. One first computes smoother and smoother versions of the original signal, obtained simply through convolution with a kernel. Now, if the original signal is "fractal", its graph has infinite length, while all regularized versions have finite length. When the smoothing parameter tends to 0, the smoothed version tends to the original signal, and its length will tend to infinity. The regularization dimension measures the speed at which this convergence to infinity takes place. In many cases, this will coincide with the usual box dimension. In general, it can be shown that the regularization dimension is more precise than the box dimension, in the sense that it is always smaller, but still larger than the Hausdorff dimension.

Wavelet dimension is estimated from the wavelet transformed data. This method is appropriate for analysis of non-stationary traces, i.e. where the variance does not remain constant with increasing length of the data set. Fractal properties are present where the wavelet power spectrum is a power law function of frequency. The Wavelet method is based on the property that Wavelet transforms of the self-affine traces have self-affine properties.

The Poincare' map is a classical tool in the study of a dynamical system around a known periodic solution. A Poincare' section or map is a device invented by Henri Poincare' for analysing systems of higher than two dimensions, by projecting the data on a two dimensional plane. The patterns that are seen in the two dimensional plane could throw light into the underlying pattern and the embedded complexities.

The statistical tests were performed using Kyplot ver. 2.0 (Koichi Yoshioka). The wavelet dimension was estimated using Benoit ver. 1.31 software (TruSoft Int'l Inc, FL, USA)

and Regularisation dimension was determined using FracLab ver 1.1 (INRIA Paris, France).

III. Result and Discussions

Figs 1 to 3 show the raw EEG signals of the Fp1-F7, Fp2-F8 and Fz-Cz leads respectively of a healthy volunteer and an encephalitis patient. No obvious differences could be seen between these two sets of signals with naked eye. In the patients, the background EEG was generally of low voltage of 5-10 microvolt amplitude and 7-8 Hz frequency with appreciable monotony of the waveforms. The response to commands for eye-opening and closure, name calls and hyperventilation were diminished. No significant asymmetry was seen between left and right side records and there was no abnormal focal regional slowing. Paroxysmal activities such as spikes or sharp waves were conspicuously absent throughout the record. Thus the EEG suggested a mild diffuse non-specific encephalopathy in all three cases.

Most medical institutions, even the advanced centers and in developed countries, lack facilities for characterizing all viral species except for the few common agents but a robust diagnosis of viral encephalitis can be made on clinical grounds itself as in our series [3]. Even virology research centers have narrow spectrums of diagnostic acumen depending upon their location and specific interests related to regional health care priorities. The patients studied befitted a clinical diagnosis of nonspecific diffuse viral encephalitis. Appropriate laboratory investigations rules out metabolic and other important causes of non-encephalitic forms of diffuse encephalopathies. The viral agent could not be identified in this particular epidemic as is often the case in most such epidemics but the diagnosis of viral encephalitis has been robust. The EEG changes in encephalitides of various viral origins have several common features, often mimicking diffuse encephalopathies [3]-[5], [7]-[9], [16]-[24].

TABLE I
Comparison of Mean of Average Values of EEGs

	Normal	Patients	t calculated	P
Fp2-F8	40.8	41.0	0.019	>0.05
Fp1-F7	24.1	26.7	0.29	>0.05
T6-O2	2.69	-9.6	0.69	>0.05
T5-O1	-5.2	2.7	0.83	>0.05
Fz-Cz	-23.6	-31.0	0.31	>0.05

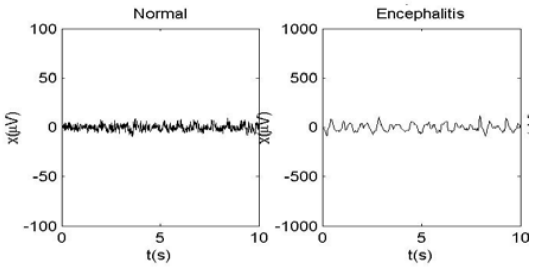


Fig. 1 Raw EEGs (Fp1-F7)

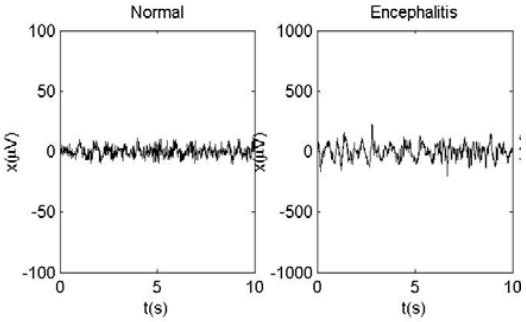


Fig. 2 Raw EEGs (Fp2-F8)

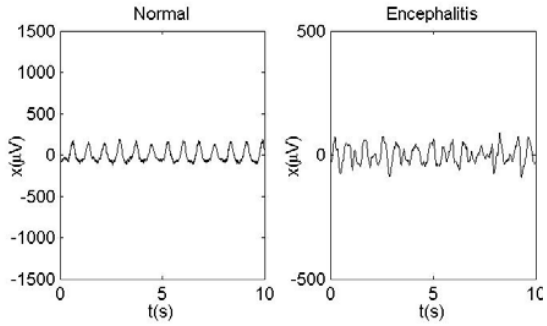


Fig. 3 Raw EEGs (Fz-Cz)

TABLE II
Comparison of Mean of Standard Deviation Values of EEGs

	Normal	Patients	t calculated	P
Fp2-F8	50.5	115.5	2.39*	<=0.05
Fp1-F7	39.7	131.9	4.52**	<=0.01
T6-O2	294.4	23.4	1.68	>0.05
T5-O1	72	19.1	1.0	>0.05
Fz-Cz	2144	59	1.9	>0.05

Table I lists the mean of the average values of EEG from various locations both for the patients and normal volunteers.

Two sample t-test indicates that there are no statistically significant difference between the average values between the two groups.

Table II lists the mean of the standard deviation values of EEG from various locations both for the patients and normal personnel. Two sample t-test indicates that statistically significant difference between the standard deviation values between the two groups are seen at Fp2-F8 and Fp1-F7 locations (P<0.05*), while no statistical difference was seen between the standard deviation values between the two groups at other places. The standard deviation (or variance) of the EEG signals at these two symmetric frontal/anterior temporal locations are significantly higher for the patients than the normal persons.

The Regularisation dimension is significantly less for the patients (average between 1.24-1.43) when compared to the normal persons (average between 1.41-1.63) for the EEG signals from all locations (P<0.01**) except for the Fz-Cz signal (P>0.05) (Table III).

TABLE III
COMPARISON OF REGULARISATION DIMENSION FOR NORMAL PERSONS AND PATIENTS.

	Fp2-F8		Fp1-F7	
	Patient	Normal	Patient	Normal
Mean	1.245	1.625	1.27	1.63
Standard deviation	0.03	0.09	0.03	0.023
t -calculated	9.98*		8.3*	
P	<=0.001		<=0.001	

	T6-O2		T5-O1	
	Patient	Normal	Patient	Normal
Mean	1.406	1.574	1.434	1.621
Standard deviation	0.085	0.102	0.09	0.101
t -calculated	3.6*		4.008*	
P	<0.01		<0.01	

	Fz-Cz	
	Patient	Normal
Mean	1.282	1.412
Standard deviation	0.0485	0.18
t -calculated	1.72	
P	>0.05	

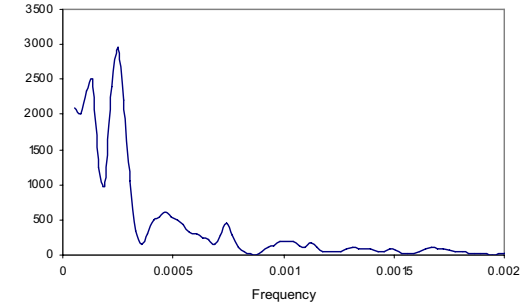
Similarly the wavelet dimension is significantly less (P < 0.05*) for the patients (1.122) when compared to the normal person (1.458) (Table IV).

TABLE IV
COMPARISON OF WAVELET DIMENSION FOR COMBINED FP2-F8 AND FP1-F7 SIGNALS (T CALCULATED = 2.075* (P < 0.05))

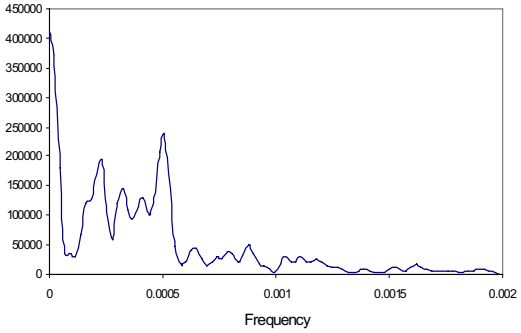
	Patient	Normal
Mean	1.122	1.458
Standard deviation	0.007	0.373

Table IV Comparison of wavelet dimension for combined Fp2-F8 and Fp1-F7 signals (t calculated = 2.075* (P < 0.05)) Fractal dimension is an indication of the spatial nature of the spectrum and a reduction in its value is an indication of decrease in chaos. A normal healthy person is expected to have a chaotic EEG and it is subdued in the case of the patients with presence of uniform patterns. A decrease in randomness for alcoholic and epileptic patients when compared to normal patients due to hyper-synchronization of EEG has been observed by researchers [12]. Lee et al [25] have observed that the correlation dimension with spatial embedding as a good discriminating statistics for differentiating EEGs of normal and schizophrenic patients. The latter were found to have lower dimensional complexity. Similarly decreased complexity of EEG patterns in Alzheimer's disease patients has been observed by Abasolo et al [26].

The Fast Fourier transform analysis of the Fp2-F8 of an encephalitis patient and a normal healthy female is shown in Fig 4 (Figs for other locations are not shown). While several dominant frequencies are observed in a normal healthy female in all the three locations, the number of dominant frequencies is less in the case of the patients indicating decrease in chaotic nature of the oscillations. The amplitude of the frequencies is an indication of the energy of the spectrum. The average total energy of the signals of the encephalitis patient is lesser than that of the normal person. Decrease in chaos and entropy has been observed in epileptic patients when compared to normal patients [27]. Decrease in EEG complexity has been observed during first episode schizophrenia leading to reduced ability to process information [28]. Fast fourier transform has been used to study various sleep patterns including REM and identify existence of scale independent behaviour [13],[29], [30].Decrease in dominant frequency have been observed interictally in epileptic patients.



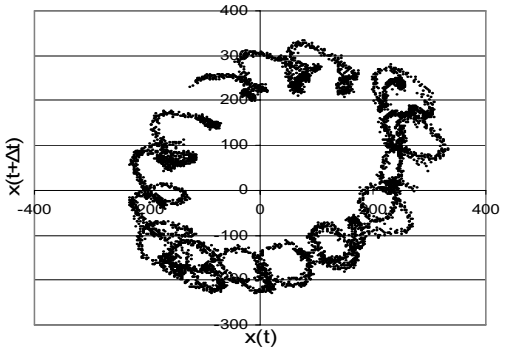
(a) patient



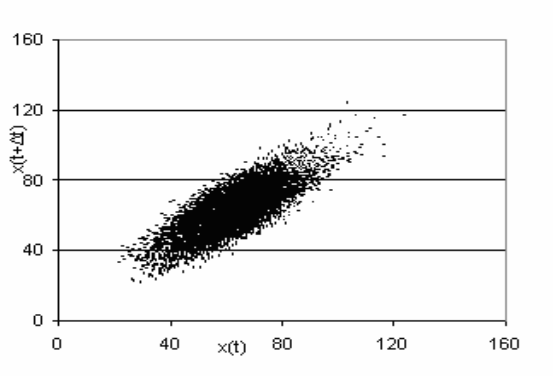
(b) Normal female

Fig. 4: Fast Fourier transform of Fp2-F8 EEG data (a) patient and (b) Normal female

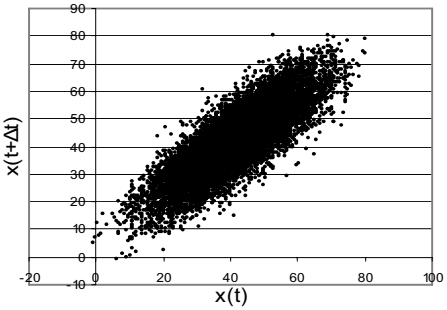
Comparison of the Poincare' maps of the Encephalitis patient with a normal healthy male and a normal healthy female reveals interesting differences. A fixed pattern (a toroidal shape) is seen in the EEG of the patient when compared to the EEG of the normal male and female persons (elliptical shape covering the entire region) at Fp2-F8 (Fig 5). The map indicates the uniformity of the EEG signals at these two cranial locations for a patient, when compared to the healthy persons. The signals of the healthy patients are chaotic hence covers the entire Ponicare' space, while that of the patients are uniform and nonrandom hence traversing only a smaller region of the 2D planar region. Decrease in complexity of EEG signals during alert eyes closed stage (α waves) when compared to alert eyes open stage (β waves) and during sleep stage 4 when compares to sleep stage 2 has been observed by Doble and Nadkar [31].



(a) Encephalitis patient



(b) Healthy male



(c) Healthy female

Fig. 5: Poincare' map of Fp2-F8 EEG data (a) Encephalitis patient, (b) healthy male and (c) healthy female

IV. Conclusion

The EEG is subdued in the case of the patients with presence of uniform patterns. This is manifested in the values of Regularisation and wavelet dimensions. Both the dimensions are less for the patients when compared to the normal person. This indicates a decrease in chaotic nature of the EEG for the patients when compared to healthy volunteers. Fourier transformation of the signals from patients shows less number of dominant frequencies when compared to normal subjects which also indicates decrease in chaos. Poincare' map also

reveals chaos in the normal subjects and a pattern in the patients. The mathematical techniques discussed in this paper appear to be a good set of tools for analyzing spatio-temporal oscillations and chaos.

APPENDIX

Fourier Transform

The Fourier transform gives the set of frequency components, which exist in our signal. Any 2π-periodic function $f(x)$ is the sum of its Fourier series

$$a_o + \sum_{k=1}^{\infty} (a_k \cos(kx) + b_k \sin(kx) \quad (1)$$

The coefficients a_o, a_k and b_k are given as

$$a_o = \frac{1}{2\pi} \int_0^{2\pi} f(x)dx$$

$$a_k = \frac{1}{\pi} \int_0^{2\pi} f(x)\cos(kx)dx$$

$$b_k = \frac{1}{\pi} \int_0^{2\pi} f(x)\sin(kx)dx$$

Wavelet transform

The wavelet transform of a continuous time signal, *x(t)*, is defined as [14]:

$$T(a,b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} x(t)\psi^* \left(\frac{t-b}{a} \right) dt \quad (2)$$

where ψ*(t) is the complex conjugate of the analysing wavelet function ψ(t), a is the dilation parameter of the wavelet and b is the location parameter of the wavelet.

Regularisation dimension

The regularisation dimension of a graph is given by the following equation

$$= 1 + \lim_{a \to 0} \frac{\log(L_a)}{-\log(a)} \quad (3)$$

Where $L_a = \int_K \sqrt{1 + f'_a(t)^2}\, dt$

Let χ (t) be a kernel function such that:

$\int \chi = 1$. Let $\chi_a(t) = \frac{1}{a}\chi(\frac{t}{a})$

Be the dilated version of χ at scale a.

Let f_a be defined as $f_a = f * \chi_a$.

Wavelet dimension

Consider n wavelet transforms each with a different scaling coefficient a_i, where s_1, s_2,..., s_n are the standard deviations from zero of the respective scaling coefficients a_i. If the ratio of the standard deviations are considered as the Hurst exponent (H) is $H=f(G_{avg})$, where f is a heuristic function which approximates the Hurst exponent by G_{avg} for stochastic self-affine traces. Generally n is assumed as equal to 4 and $a_i=2i$, for i=0, 1, 2, 3. The fractal dimension = 2-H. In the software used here the mother wavelet is a step function.

$G_1=s_1/s_2$, $G_2=s_2/s_3$,..., $G_{n-1}=s_{n-1}/s_n$

If G_{avg} is average of these ratios then,

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