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A Mathematical Bivariate Generalized Poisson Model for Cortisol Awakening Response with Multiple Sclerosis in Humans

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Abstract:- In this paper, we discuss about the bivariate generalized Poisson distribution for the cortisol awakening response and multiple sclerosis in humans. Dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis has been frequently been reported in multiple sclerosis (MS). So far, HPA axis function in MS has predominantly been studied under pharmacological stimulation which is associated with a series of methodological caveats. Knowledge of circadian cortisol patterns and cortisol awakening response (CAR) is still limited. We have found the probability generating function and moment generating function for cortisol awakening response and the corresponding mathematical figures 3.1 to 3.6 have been given in section 3.

Keywords:- Corticotropin Releasing Hormone, Cortisol, Multiple Sclerosis, Cortiol Awakening Response. 2010 AMS Classification: 62HXX, 60EXX.

I. MATHEMATICAL MODEL:

Bivariate Generalized Poisson distribution:

In this paper, we discuss the Bivariate generalized Poisson distribution. The distribution is derived from the generalized Poisson distribution [1, 3] using the Trivariate reduction method. In this, we present some properties of BGPD such as Probability Generating Function (PGF) and Moment Generating Function (MGF).

(1.1) Probability Generating Function (PGF):

The pgf of a random variable N is defined by $\prod_N(t) = E(t^N)$ and the pgf of the pair of random variables (X, Y) is $\prod(t_1, t_2) = E({t_1}^X\ {t_2}^Y)$.

Let the pgf 's of the random variables under consideration be $\prod_i(t)$, i=1,2,3.

Then the joint pgf of (X, Y) is $\prod(t_1, t_2) = \prod_1(t_1)\prod_2(t_2)\prod_3(t_1t_2)$. (1.1.1).

For simplicity, we assume the parameters $\theta_t > 0, t = 1,2,3$.

Ambagaspitiya and Balakrishnan [1] have expressed the pgf of the GPD in terms of Lambert's W function when $\theta > 0$, as follows.

$$\prod_N(t) = exp\left\{\frac{-\lambda}{\theta}\left[W\left(-\theta z\, exp(-\theta)\right) + \theta\right]\right\}, \quad (1.1.2)$$

Where the Lambert's W function is defined [5] as $W(x)\exp\left(W(x)\right) = x$.

From (1.1.1) and (1.1.2), the pgf of (X, Y) is

$$\prod(t_1, t_2) = exp\left\{\frac{-\lambda_1}{\theta_1}W\left(-\theta_1 t_1 exp(-\theta_1)\right) - \frac{\lambda_2}{\theta_2}W\left(-\theta_2 t_2 exp(-\theta_2)\right) - \frac{\lambda_3}{\theta_3}W(-\theta_3 t_1 t_2 \exp(-\theta_3)) - \lambda\right\} \quad (1.1.3)$$

with $\lambda = \lambda_1 + \lambda_2 + \lambda_3$ [10].

1.2: Moment Generating Function (MGF):

If the mgf of N_t is $M_i(t), i = 1,2,3,$ then the mgf of (X, Y) is

$$M(t_1, t_2) = M_1(t_1)M_2(t_2)M_3(t_1 + t_2) \quad (1.2.1)$$

The mgf of the GPD, when $\theta > 0$, is given by

$$M_N(t) = exp\left\{\frac{-\lambda}{\theta}\left[W(-\theta \exp(-\theta + t)) + \theta\right]\right\} \quad (1.2.2)$$

Using (1.2.1) and (1.2.2) we get

$$M(t_1, t_2) = exp\left\{\frac{-\lambda_1}{\theta_1}W\left(-\theta_1 exp(-\theta_1 + t_1)\right) - \frac{\lambda_2}{\theta_2}W\left(-\theta_2 exp(-\theta_2 + t_2)\right) - \frac{\lambda_3}{\theta_3}W\left(-\theta_3 exp(\theta_3 + t_1 + t_2)\right) - \lambda\right\}$$

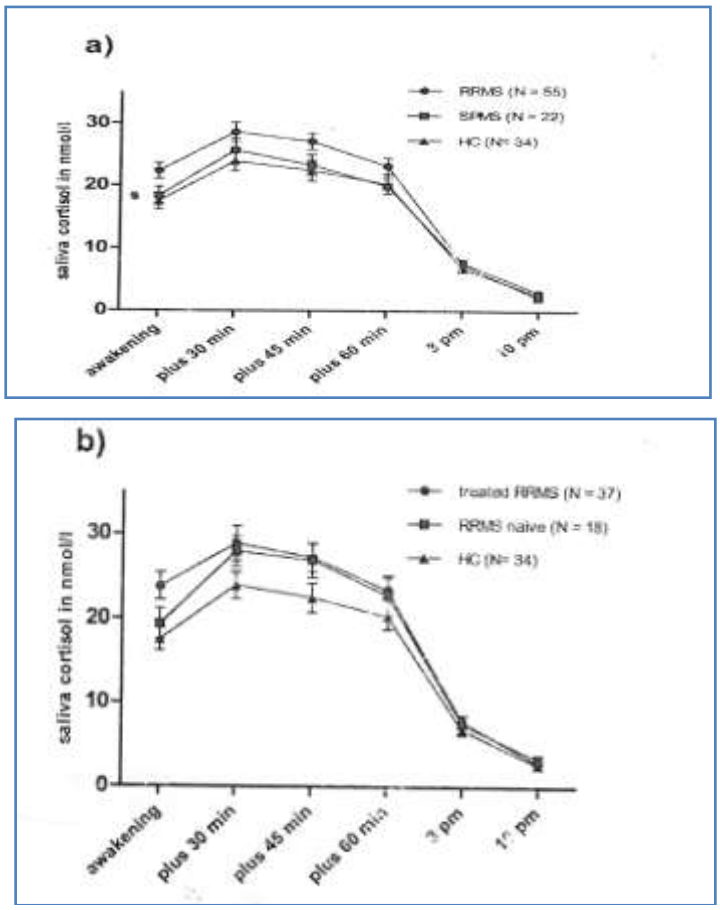
II. APPLICATION

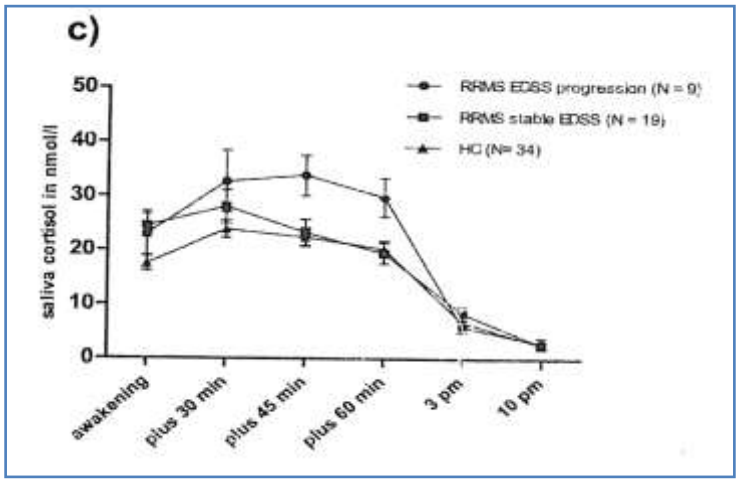
The cortisol awakening response (CAR) is a well described phenomenon which is characterized by a pronounced increase of cortisol within 20 to 30 minutes after awakening [2, 6]. While the precise mechanisms are still not entirely understood, CAR seems to be controlled by limbic regions [11]. It is further modulated by various factors such as genetic polymorphisms, stressful experience, affective symptoms and inflammatory states [7]. Independently of the underlying modulating mechanisms, an elevated CAR indicates a hyperactive hypothalamus- pituitary-adrenal (HPA) axis with an increased diurnal cortisol release.

A hyperactive HPA axis has often been reported in multiple sclerosis (MS): in post mortem studies enlarged adrenals as well as increased activity of corticotrophin-releasing-hormone (CRH) producing cells within the hypothalamus have been found. In response to intravenous administration of CRH, cortisol release was increased in MS patients compared to healthy control subjects. HPA axis function also seems to be linked to radiological as well as clinical aspects: increased cortisol response to CRH is associated with gadolinium enhancing lesions, a marker for acute central nervous system inflammation in MS. Increased adrenocortocotropic hormone (ACTH) response to CRH administration has been linked to disease progression and cognitive dysfunction [12].

We hypothesize that MS patients express an elevated diurnal cortisol release when compared to healthy control (HC) subjects. Relapsing-remitting (RRMS) as well as secondary-progressive (SPMS) MS patients are studied in order to identify a possible link between circadian cortisol release patterns disease course as well as disease duration. Finally, we expect diurnal cortisol patterns to be associated with treatment, disease progression, affective symptoms and perceived stressful experience.

Our data indicates that RRMS patients but not SPMS patients express a significantly greater CAR when compared to age and sex matched HC subjects. Elevated levels of ACTH and cortisol in response to CRH administration in MS patients have frequently reported and endocrine changes seem to be associated disease progression. HPA axis activity is most pronounced in RRMS patients during acute relapse. Clinically stable RRMS patients express intermediate levels while SPMS patients express only moderately elevated circadian cortisol levels. Increased circadian HPA axis activation in RRMS patients therefore reflect a compensatory mechanism in response to increased central as well as systemic inflammation. This interpretation is in line with our finding that only RRMS patients with EDSS progression but not stable RRMS patients express a significantly greater CAR when compared to HC subjects.





Mean circadian saliva cortisol and AUC awakening. (a) RRMS/SPMS patients and HC subjects. (b) Treated RRMS/treatment naïve RRMS patients and HC subjects. (c) RRMS with EDSS progression ≥ 0.5 and HC subjects.

III. MATHEMATICAL RESULTS

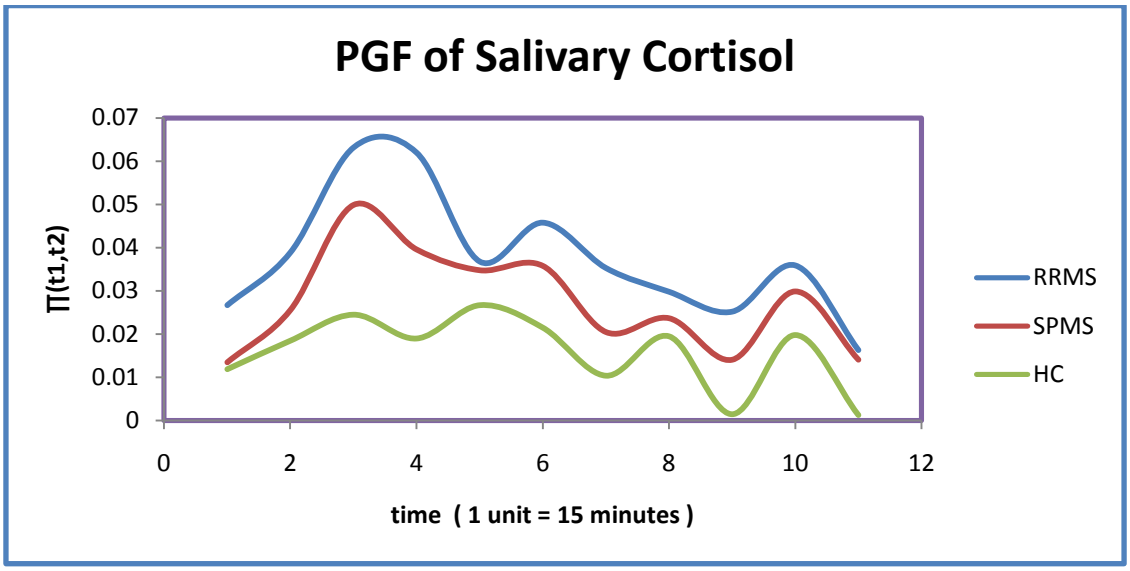


Fig 3.1

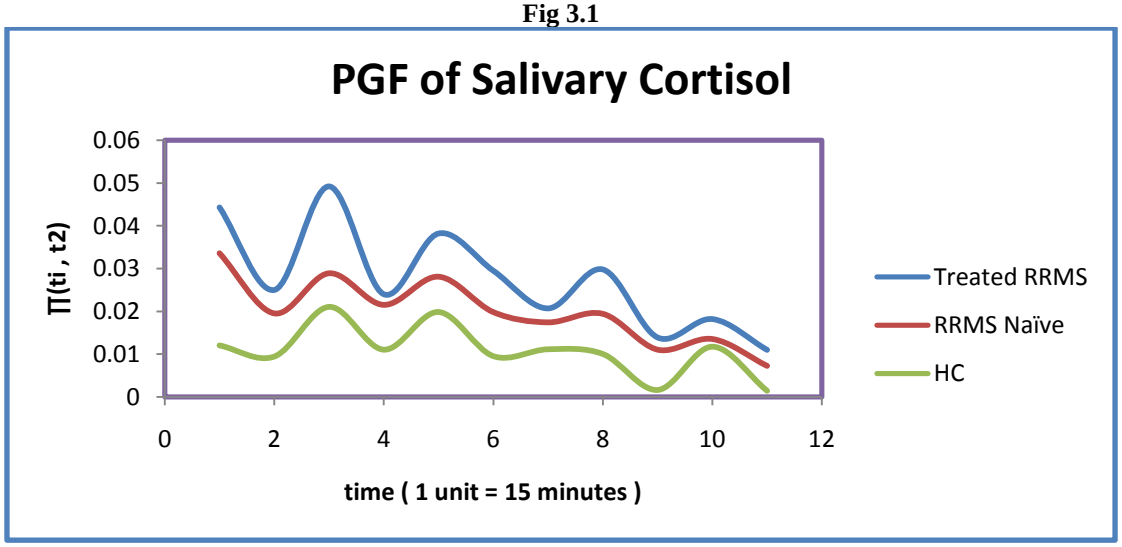


Fig 3.2

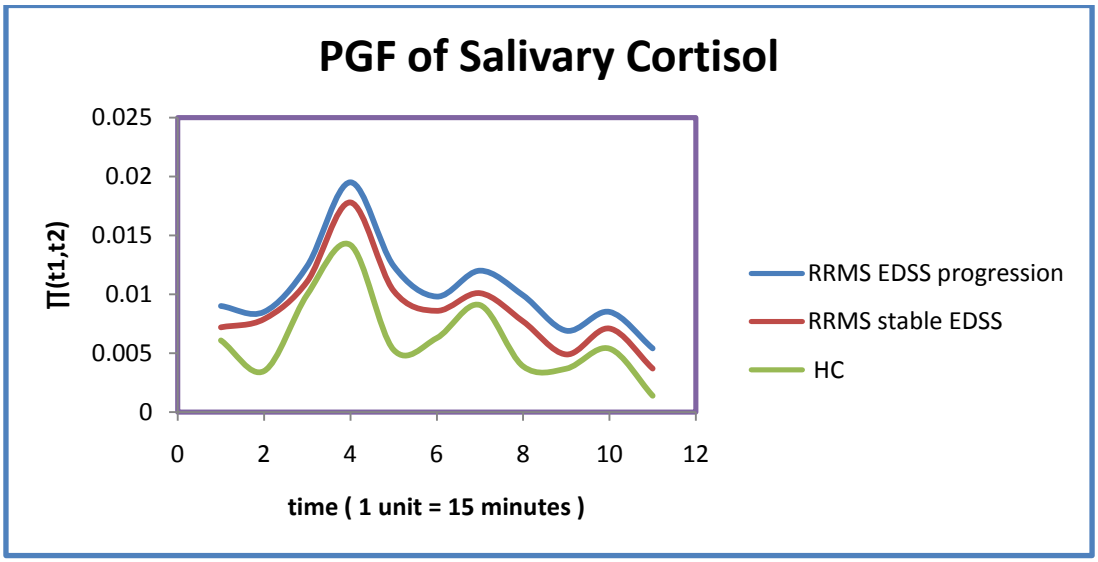


Fig 3.3

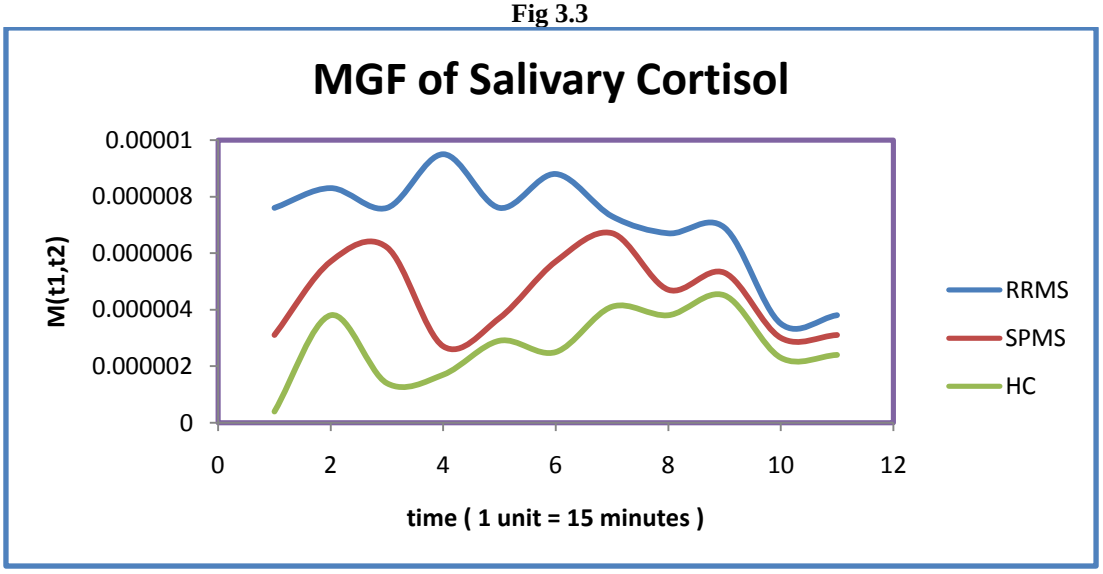


Fig 3.4

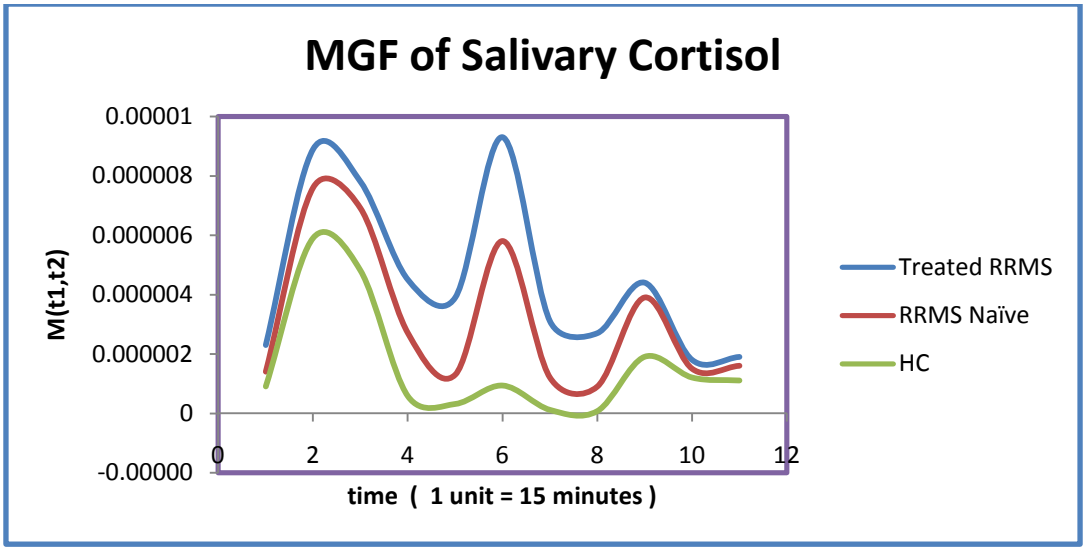


Fig 3.5

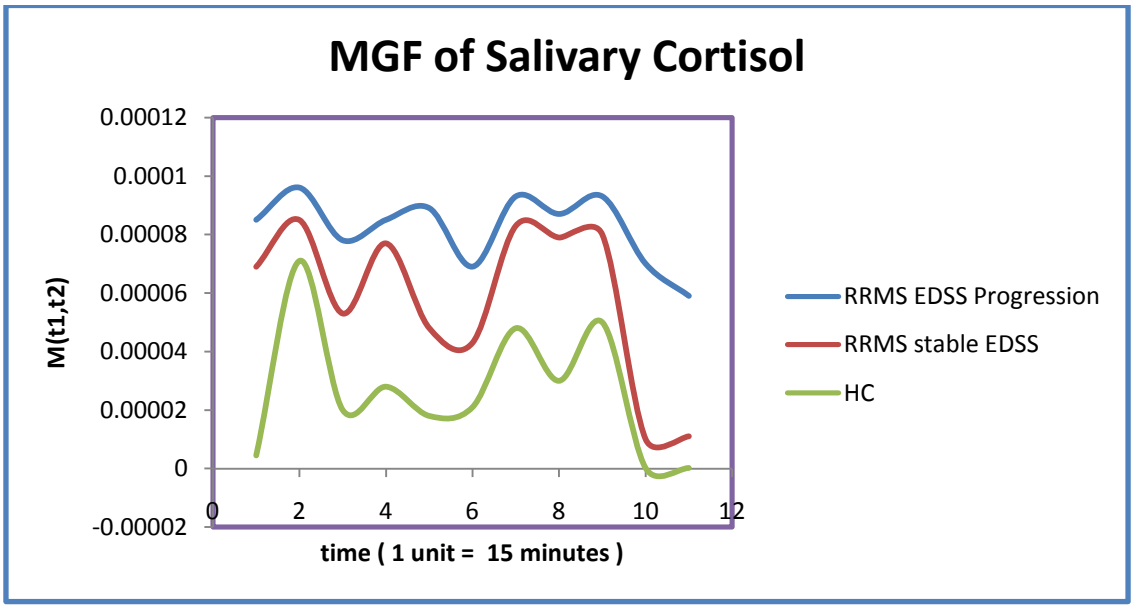


Fig 3.6

IV. CONCLUSION

Realization of the process follows birth and death process. Each bits of curve follows birth and death process with different intensities in both **PGF** and **MGF** of salivary cortisol, in all the three cases. Our mathematical figures reveal that in the first case of salivary cortisol the probability generating function is higher for the RRMS patients than the SPMS and HC patients. In the second case, the treated RRMS patients have more responsible that is with much cortical awakening response than the RRMS naïve and HC patients. In the third case, RRMS EDSS Progression patients have more cortical awakening response than the RRMS stable EDSS and HC patients. In the case of moment generating function, the RRMS patients have very significant response than the SPMS and HC patients. In the second case, the treated RRMS patients show more response than the RRMS naïve and HC patients. In the third case, similar to the first case, RRMS EDSS progression patients reveal more cortical response significantly than the RRMS stable EDSS and HC patients.

These findings indicate that circadian cortisol response is predominantly affected by the acute disease state and not so much by previously accumulated deficits and disease duration. This coincides with the medical conclusions that only RRMS patients with EDSS progression but not stable RRMS patients expressed a significantly greater CAR when compared to HC subjects. But in our Mathematical model, we can find the time of progression and the time of stability for the different cases.

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