

Case Report

Salivary Alpha-Amylase Activity Levels in Catatonic Schizophrenia Decrease after Electroconvulsive Therapy

Misako Kanayama , Tsuyoshi Miyaoka , Tomoko Araki, Maiko Hayashida ,
Sadayuki Hashioka, and Jun Horiguchi

Department of Psychiatry, Shimane University of Medicine, 89-1 Enyacho, Izumo 6938501, Japan

Correspondence should be addressed to Misako Kanayama; misakoka@med.shimane-u.ac.jp

Received 7 December 2017; Revised 30 January 2018; Accepted 22 February 2018; Published 10 May 2018

Academic Editor: Toshiya Inada

Copyright © 2018 Misako Kanayama et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Dysfunction of the autonomic nervous system (ANS) in schizophrenia has been detected by electrophysiological methods, but the underlying mechanisms remain unknown. Several studies have suggested that measuring salivary alpha-amylase activity levels is useful for evaluating the ANS activity and that sAA levels increase in schizophrenia and correlate with Brief Psychiatric Rating Scale (BPRS) scores. However, no study has examined the relationship between sAA activity levels and symptoms of schizophrenia with catatonic state. **Methods.** We present the case of a 59-year-old female with persistent catatonic schizophrenia treated by electroconvulsive therapy. We evaluated the ANS activity by measuring sAA activity levels before and after ECT, and we evaluated her symptoms using the BPRS and Bush–Francis Catatonia Rating Scale (BFCRS). **Results.** ECT was highly effective and BPRS and BFCRS scores substantially decreased. sAA activity levels decreased from 125 kU/l to 33 kU/l. **Conclusions.** sAA activity levels could be a potential biomarker of schizophrenia with catatonic state.

1. Introduction

The pathology of schizophrenia remains unknown, and a relevant biomarker remains to be identified. Various studies have been conducted to address this, including studies on the autonomic nervous system (ANS) [1–7]. These studies have indicated a dysfunction of the ANS in patients with schizophrenia [1, 2, 5–8].

Measurement of salivary alpha-amylase [9] activity levels is reportedly useful for evaluating activity of the ANS [10–13], and a simple, noninvasive appliance has been recently developed to measure sAA activity levels [14, 15]. sAA activity levels of patients with schizophrenia have been reported to be higher than those of controls, and these levels have been associated with the severity of symptoms in patients with schizophrenia [16, 17].

However, only one study has examined the change in diachronic sAA activity levels before and after treatment [18]: it was a case report of a patient treated with electroconvulsive therapy [19] for schizophrenia; however, only one psychiatric symptoms rating scale, the Brief Psychiatric Rating Scale

(BPRS), was used. Using ECT, the symptoms of catatonia are easier to heal than the other symptoms of schizophrenia; thus, we examined Bush–Francis Catatonia Rating Scale (BFCRS). To the best of our knowledge, no previous report has checked the relationship between sAA activity levels and BFCRS.

Here, we discuss the case of a patient with catatonic schizophrenia treated by ECT. Because persistent catatonia was an important element, we assessed her symptoms using the BFCRS, a gold standard scale for catatonia [20–23], and examined the relationship between sAA activity levels and BFCRS scores for catatonia before and after treatment.

2. Case Presentation

A 59-year-old woman was admitted to our psychiatric department for ECT. She had been diagnosed with schizophrenia at the age of 17 years and had taken antipsychotic drugs for 42 years. She had no history of alcohol consumption, drug use, or epileptic seizures. One day, at the age of 55 years, she lay on a road and was unable to move or speak due to a catatonic state. She was immediately admitted to a hospital.

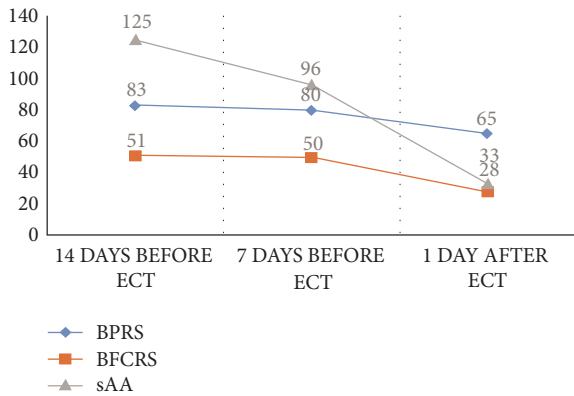


FIGURE 1: The relationship between the patient's salivary alpha-amylase activity levels (kU/l) and scores for the Brief Psychiatric Rating Scale (BPRS) and Bush-Francis Catatonia Rating Scale (BFCRS).

However, medicines proved ineffective, despite attempting several types of second-generation antipsychotic drugs and benzodiazepines. Her white blood-cell counts were too low for clozapine use. Thus ECT was recommended, and she was transferred to our hospital, the only hospital in the area to offer ECT.

She exhibited severe catatonia as well as many other psychotic symptoms, such as hallucination, delusion, and negative symptoms. She was taking risperidone 9 mg daily without side effects for nearly 10 years. Besides she had been taking magnesium oxide 1.2g and sennoside 36 mg daily for constipation for many years. The minor tranquilizer was stopped for ECT and was no longer necessary after ECT. We performed ECT, applied three times a week for a total of 14 sessions. Thiopental and ketamine were used to induce anesthesia.

We evaluated her symptoms by BPRS and BFCRS (23 items) at 14 and 7 days before ECT and after the course of ECT was complete. On the same days, we measured her sAA activity levels with a colorimetric salivary biosensor (Nipro Co., Japan). In order to eliminate the effects of hospitalization, we measured sAA activity levels again not only immediately after hospitalization but also just before ECT. Thus, we measured her sAA activity levels twice before ECT. The saliva samples were collected in the morning following a 10-min rest on a chair or bed, at least 2 h after the last meal and tooth-brushing.

ECT was extremely successful, and her symptoms considerably improved after the 14 sessions, with remarkable reductions in BPRS and BFCRS scores. Her BPRS and BFCRS scores decreased from 83 to 65 and from 51 to 28, respectively. Her sAA activity levels also substantially decreased from 125 kU/l to 33 kU/l. Figure 1 shows the changes in the BPRS, BFCRS, and sAA activity levels before and after ECT.

3. Discussion

Here, we investigated the ANS of a patient with persistent catatonic schizophrenia before and after ECT by measuring

sAA activity levels. This decreased in a similar manner to the improvement in the BPRS and BFCRS scores before and after ECT. To the best of our knowledge, this is the first report to examine the relationship between sAA activity levels and BFCRS.

Many studies have investigated the ANS, using various electrophysiological methods such as electrodermal measures, heart rate analysis, and measuring blood or salivary cortisol levels [3, 4, 8, 24, 25]. Cortisol is similar to sAA activity levels in reflection to stress. Measuring blood cortisol involves needle prick. Therefore, great stress of pricking needles at the time of blood collection was mixed as a bias to stress of psychosis itself. Salivary cortisol is too difficult to collect from patients with severe psychiatric symptoms. In this study, we used sAA activity levels to evaluate the ANS. Every measurement method has advantages and disadvantages, but sAA, which can be measured easily and quickly, is very useful when the mental symptoms are badly cooperative like this time.

The sAA activity levels are considered to be a noninvasive biomarker for assessing mental stress [11–13, 26, 27], and it has been suggested that it reflects the activity of the sympathetic-adrenal-medullary system [12, 26, 28–31]. Blood pressure, heart rate, plasma catecholamine level, and activities of the sympathetic nervous system in heart rate variability have been shown to correlate with sAA activity levels [32, 33]. However, the use of sAA activity levels has its weaknesses. There have been disagreements over whether high sAA activity reflects the loss of vagal activity or high activity of the sympathetic nervous system [28, 34]. In either case, it is believed to represent a function of sympathetic nerve activity. Beta-blockers, which block the sympathetic nervous system, have been shown to prevent fluctuations in sAA activity levels [31], again suggesting that sAA activity represents a function of sympathetic nerve activity. There has also been some controversy over how to collect saliva [34–37]. For the monitor used in this study, saliva was collected using a paper filter, with the sAA activity level on the paper measured immediately. Overall, this has been considered a reliable method [14, 15, 36].

Various previous studies have suggested a dysfunction of the ANS of patients with schizophrenia [4–7, 25]. However, the underlying mechanisms remain unclear. Bar et al. measured heart rate variability and reported that patients with acute schizophrenia showed dysfunction of the ANS activity, particularly parasympathetic activity [2, 8]. Fujibayashi et al. also indicated that there may be depressed activity of the ANS in patients with schizophrenia [38]. Recently, meta-analysis of autonomic nervous function by heart rate variability (HRV) in patients with mental illness was performed [1]. In this study, 1692 patients with psychiatric disorders, including schizophrenia, and 1639 controls were analyzed. Of the patient group, 812 people were not medicated, and 880 were medicated. As a result, it was confirmed that autonomic nervous function was declining dominantly in psychiatric disorders patients under non-medication compared with healthy group. They concluded that the decline of the autonomic nerve was observed in schizophrenia, regardless of medicine. Our report, although

the method used was different, had the same result as these results.

In addition, our colleague observed high sAA levels in such patients [17] and showed that sAA activity levels were proportional to the severity of psychosis, as measured by the BPRS [16, 39]. Our case supported this finding. In other words, the reason why sAA activity levels were high before ECT this time could be because schizophrenia symptoms were severe.

Several studies have investigated the effect of medication on the activity of the ANS [40–43]. However, in our case, there was no change in the medication taken by our patient before and after ECT. In addition, she did not take other antipsychotics or minor tranquilizers. The laxative that she was taking was not changed before and after the ECT. To the best of our knowledge, no studies have been performed suggesting that larvae affect autonomic nerves. Therefore, further examination might be required.

This patient experienced a decrease in the BFCRS score following ECT, and at the same time, her sAA activity levels decreased from high to normal. This might suggest that the sAA activity levels were related to the severity of symptoms of catatonia. Furthermore, our patient's catatonia had been persistent, lasting more than 4 years. If a long-standing disorder of the ANS induced an irreversible change in the nervous systems, sAA activity levels would not be expected to change when symptoms were relieved by ECT. Our findings therefore demonstrated that no irreversible change had occurred as a result of the patient's persistent dysfunction of the ANS. The results of our case support the previous review [6]. That is, autonomic abnormality of schizophrenia may be due to stress caused by the symptoms rather than the disease itself.

There is one report about the relationship between sAA activity levels and the psychiatric symptoms of schizophrenia [18]. In that report, sAA activity levels declined with the improvement of mental symptoms, and it is same as our report, which indicates reproducibility. Additionally, in the present case, the patient experienced a decrease in the BFCRS score following ECT, and concurrently her sAA activity levels decreased from high to normal.

We have discussed one curious thing. Between 14 days and 7 days before the ECT, sAA activity levels decreased intensely though BPRS and BFCRS scores decreased slightly. It was intriguing because measurement conditions at 14 days and 7 days were completely unchanged. It might reflect the gradually declined stress of being transferred from other hospitals to our hospital in addition to ANS disorder due to psychic symptoms themselves. We need to investigate by collecting more cases.

This report has some limitations. We examined the ANS only by measuring sAA activity levels, although heart rate variability is also a useful method. It is unclear whether sAA change was caused by improvement of catatonia, improvement of psychosis, or effect of ECT. There were several studies on the influence of ECT on ANS (no study by sAA). According to them, parasympathetic nerves were stimulated by ECT [44–47]. It was also pointed out that strength of stimulation of ANS may be related to the effect of ECT [46].

However, those studies investigated the impact of several minutes after ECT. As far as we examined, we could not find a study that examined the effects of the following day as our case. Those studies showed as limitations that some of anesthetic drugs were said to stimulate sympathetic nerves and others to stimulate parasympathetic nerves [46, 48]. However, since each drug had a half-life of several hours, it could be hard to think that it continued to exert influence on our study, the following day as well. Next limitation is that our report discusses a single case and only one disease. Further research is needed to investigate the pathology and establish biomarkers of schizophrenia with catatonic state.

We reported the association among sAA activity levels, schizophrenia symptoms, and catatonia in only one case. Our findings suggested that sAA activity level might be a potential biomarker for catatonic schizophrenia.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank all doctors and staff of the Department of Psychiatry, Shimane University of Medicine for their help with ECT.

References

- [1] G. A. Alvares, D. S. Quintana, I. B. Hickie, and A. J. Guastella, "Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis," *Journal of Psychiatry & Neuroscience*, vol. 41, no. 2, pp. 89–104, 2016.
- [2] K. J. Bar, A. Letzsch, T. Jochum, G. Wagner, W. Greiner, and H. Sauer, "Loss of efferent vagal activity in acute schizophrenia," *Journal of Psychiatric Research*, vol. 39, no. 5, pp. 519–527, 2005.
- [3] A. M. Schell, M. E. Dawson, A. Rissling et al., "Electrodermal predictors of functional outcome and negative symptoms in schizophrenia," *Psychophysiology*, vol. 42, no. 4, pp. 483–492, 2005.
- [4] R. A. Schiffer, M. Sigal, and M. Mintz, "Delayed habituation of the skin-conductance orienting response correlates with impaired performance on the Wisconsin Card Sorting Task in schizophrenia," *Psychiatry Research*, vol. 65, no. 2, pp. 107–112, 1996.
- [5] S. A. Akar, S. Kara, F. Latifoğlu, and V. Bilgiç, "Analysis of heart rate variability during auditory stimulation periods in patients with schizophrenia," *Journal of Clinical Monitoring and Computing*, vol. 29, no. 1, pp. 153–162, 2015.
- [6] J. M. Montaquila, B. J. Trachik, and J. S. Bedwell, "Heart rate variability and vagal tone in schizophrenia: A review," *Journal of Psychiatric Research*, vol. 69, pp. 57–66, 2015.
- [7] D. S. Quintana, L. T. Westlye, T. Kaufmann et al., "Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls," *Acta Psychiatrica Scandinavica*, vol. 133, no. 1, pp. 44–52, 2016.
- [8] K.-J. Bar, K. Wernich, S. Boettger et al., "Relationship between cardiovagal modulation and psychotic state in patients with

- paranoid schizophrenia," *Psychiatry Research*, vol. 157, no. 1-3, pp. 255–257, 2008.
- [9] E. Schwarz, J. Maukonen, T. Hyytiäinen et al., "Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response," *Schizophrenia Research*, 2016.
- [10] N. Rohleder and U. M. Nater, "Determinants of salivary α -amylase in humans and methodological considerations," *Psychoneuroendocrinology*, vol. 34, no. 4, pp. 469–485, 2009.
- [11] S. Schumacher, C. Kirschbaum, T. Fydrich, and A. Ströhle, "Is salivary alpha-amylase an indicator of autonomic nervous system dysregulations in mental disorders?—A review of preliminary findings and the interactions with cortisol," *Psychoneuroendocrinology*, vol. 38, no. 6, pp. 729–743, 2013.
- [12] U. M. Nater, N. Rohleder, J. Gaab et al., "Human salivary alpha-amylase reactivity in a psychosocial stress paradigm," *International Journal of Psychophysiology*, vol. 55, no. 3, pp. 333–342, 2005.
- [13] Y. Noto, T. Sato, M. Kudo, K. Kurata, and K. Hirota, "The relationship between salivary biomarkers and state-trait anxiety inventory score under mental arithmetic stress: a pilot study," *Anesthesia & Analgesia*, vol. 101, no. 6, pp. 1873–1876, 2005.
- [14] M. Yamaguchi, T. Kanemori, M. Kanemaru, N. Takai, Y. Mizuno, and H. Yoshida, "Performance evaluation of salivary amylase activity monitor," *Biosensors and Bioelectronics*, vol. 20, no. 3, pp. 491–497, 2004.
- [15] M. Yamaguchi, J. Wakasugi, and J. Sakakima, "Competitive and product inhibition-based α -amylase activity analysis method," *Clinical Biochemistry*, vol. 41, no. 4-5, pp. 325–330, 2008.
- [16] M. Ieda, T. Miyaoka, R. Wake et al., "Evaluation of autonomic nervous system by salivary alpha-amylase level and heart rate variability in patients with schizophrenia," *European Archives of Psychiatry and Clinical Neurosciences*, vol. 264, no. 1, pp. 83–87, 2014.
- [17] T. Inagaki, T. Miyaoka, S. Okazaki et al., "High salivary alpha-amylase levels in patients with schizophrenia: A pilot study," *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 34, no. 4, pp. 688–691, 2010.
- [18] M. Ieda, T. Miyaoka, K. Kawano, R. Wake, T. Inagaki, and J. Horiguchi, "May Salivary Alpha-Amylase Level Be a Useful Tool for Assessment of the Severity of Schizophrenia and Evaluation of Therapy? A Case Report," *Case Reports in Psychiatry*, vol. 2012, pp. 1–4, 2012.
- [19] J. K. Goodrich, J. L. Waters, A. C. Poole et al., "Human genetics shape the gut microbiome," *Cell*, vol. 159, no. 4, pp. 789–799, 2014.
- [20] G. Bush, M. Fink, G. Petrides, F. Dowling, and A. Francis, "Catatonia. I. Rating scale and standardized examination," *Acta Psychiatrica Scandinavica*, vol. 93, no. 2, pp. 129–136, 1996.
- [21] B. T. Carroll et al., "Katatonia: a new conceptual understanding of catatonia and a new rating scale," *Psychiatry (Edgmont)*, vol. 5, no. 12, pp. 42–50, 2008.
- [22] R. Kirkhart, N. Ahuja, and J. W. Lee, "The detection and measurement of catatonia," *Psychiatry*, vol. 4, no. 9, pp. 52–56, 2007.
- [23] E. Wong, G. S. Ungvari, S. Leung, and W. Tang, "Rating catatonia in patients with chronic schizophrenia: Rasch analysis of the Bush–Francis Catatonia Rating Scale," *International Journal of Methods in Psychiatric Research*, vol. 16, no. 3, pp. 161–170, 2007.
- [24] L. M. Williams, P. Das, A. W. Harris et al., "Dysregulation of Arousal and Amygdala-Prefrontal Systems in Paranoid Schizophrenia," *The American Journal of Psychiatry*, vol. 161, no. 3, pp. 480–489, 2004.
- [25] M. Toichi, Y. Kubota, T. Murai et al., "The influence of psychotic states on the autonomic nervous system in schizophrenia," *International Journal of Psychophysiology*, vol. 31, no. 2, pp. 147–154, 1999.
- [26] U. M. Nater and N. Rohleder, "Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research," *Psychoneuroendocrinology*, vol. 34, no. 4, pp. 486–496, 2009.
- [27] N. Takai, M. Yamaguchi, T. Aragaki, K. Eto, K. Uchihashi, and Y. Nishikawa, "Effect of psychological stress on the salivary cortisol and amylase levels in healthy young adults," *Archives of Oral Biology*, vol. 49, no. 12, pp. 963–968, 2004.
- [28] E. B. Gordis, D. A. Granger, E. J. Susman, and P. K. Trickett, "Asymmetry between salivary cortisol and α -amylase reactivity to stress: Relation to aggressive behavior in adolescents," *Psychoneuroendocrinology*, vol. 31, no. 8, pp. 976–987, 2006.
- [29] G. B. Proctor and G. H. Carpenter, "Regulation of salivary gland function by autonomic nerves," *Autonomic Neuroscience: Basic & Clinical*, vol. 133, no. 1, pp. 3–18, 2007.
- [30] S. Shirasaki et al., "Correlation between salivary alpha-amylase activity and pain scale in patients with chronic pain," *Regional Anesthesia and Pain Medicine*, vol. 32, no. 2, pp. 120–123, 2007.
- [31] A. van Stegeren, N. Rohleder, W. Everaerd, and O. T. Wolf, "Salivary alpha amylase as marker for adrenergic activity during stress: effect of betablockade," *Psychoneuroendocrinology*, vol. 31, no. 1, pp. 137–141, 2006.
- [32] R. T. Chatterton Jr. et al., "Salivary alpha-amylase as a measure of endogenous adrenergic activity," *Clinical Physiology*, vol. 16, no. 4, pp. 433–448, 1996.
- [33] N. Rohleder, U. M. Nater, J. M. Wolf, U. Ehlert, and C. Kirschbaum, "Psychosocial stress-induced activation of salivary alpha-amylase: an indicator of sympathetic activity?" *Annals of the New York Academy of Sciences*, vol. 1032, pp. 258–263, 2004.
- [34] J. A. Bosch, E. C. I. Veerman, E. J. de Geus, and G. B. Proctor, "A-Amylase As A Reliable And Convenient Measure Of Sympathetic Activity: Don't start salivating just yet!," *Psychoneuroendocrinology*, vol. 36, no. 4, pp. 449–453, 2011.
- [35] K. Obayashi, "Salivary mental stress proteins," *Clinica Chimica Acta*, vol. 425, pp. 196–201, 2013.
- [36] M. Yamaguchi, M. Deguchi, J. Wakasugi et al., "Hand-held monitor of sympathetic nervous system using salivary amylase activity and its validation by driver fatigue assessment," *Biosensors and Bioelectronics*, vol. 21, no. 7, pp. 1007–1014, 2006.
- [37] J. A. Bosch, "The use of saliva markers in psychobiology: Mechanisms and methods," *Monographs in Oral Science*, vol. 24, pp. 99–108, 2014.
- [38] M. Fujibayashi, T. Matsumoto, I. Kishida et al., "Autonomic nervous system activity and psychiatric severity in schizophrenia," *Psychiatry and Clinical Neurosciences*, vol. 63, no. 4, pp. 538–545, 2009.
- [39] T. Inagaki, M. Ieda, S. Yamashita, T. Miyaoka, and J. Horiguchi, "Salivary Alpha-Amylase Reactivity under Psychophysiological Stress. A Nonverbal Communication Measurement Tool?" *Journal of Behavioral and Brain Science*, vol. 01, no. 01, pp. 12–15, 2011.
- [40] M. Miyauchi, I. Kishida, A. Suda et al., "Association of the cholinergic Muscarinic M2 receptor with autonomic nervous

- system activity in patients with schizophrenia on high-dose antipsychotics,” *Neuropsychobiology*, vol. 74, no. 1, pp. 60–67, 2016.
- [41] Y. Iwamoto, C. Kawanishi, I. Kishida et al., “Dose-dependent effect of antipsychotic drugs on autonomic nervous system activity in schizophrenia,” *BMC Psychiatry*, vol. 12, article no. 199, 2012.
- [42] S. Hattori, I. Kishida, A. Suda et al., “Effects of four atypical antipsychotics on autonomic nervous system activity in schizophrenia,” *Schizophrenia Research*, 2017.
- [43] T. Rechlin, D. Claus, and M. Weis, “Heart rate variability in schizophrenic patients and changes of autonomic heart rate parameters during treatment with clozapine,” *Biological Psychiatry*, vol. 35, no. 11, pp. 888–892, 1994.
- [44] S. B. Rowny, Y. M. Cycowicz, S. M. McClintock, M. D. Truesdale, B. Lubner, and S. H. Lisanby, “Differential heart rate response to magnetic seizure therapy (MST) relative to electroconvulsive therapy: A nonhuman primate model,” *NeuroImage*, vol. 47, no. 3, pp. 1086–1091, 2009.
- [45] Y. Suzuki, M. Miyajima, K. Ohta et al., “A Triphasic Change of Cardiac Autonomic Nervous System during Electroconvulsive Therapy,” *Journal of ECT*, vol. 31, no. 3, pp. 186–191, 2015.
- [46] K.-J. Bär, A. Ebert, M. K. Boettger et al., “Is successful electroconvulsive therapy related to stimulation of the vagal system?” *Journal of Affective Disorders*, vol. 125, no. 1-3, pp. 323–329, 2010.
- [47] D. M. Dhossche, “Vagal intimations for catatonia and electroconvulsive therapy,” *Journal of ECT*, vol. 30, no. 2, pp. 111–115, 2014.
- [48] C. Hoyer, L. Kranaster, C. Janke, and A. Sartorius, “Impact of the anesthetic agents ketamine, etomidate, thiopental, and propofol on seizure parameters and seizure quality in electroconvulsive therapy: A retrospective study,” *European Archives of Psychiatry and Clinical Neurosciences*, vol. 264, no. 3, pp. 255–261, 2014.



Hindawi

Submit your manuscripts at www.hindawi.com

