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Pitout JDD, Church DL, Gregson DB, Chow BL, McCracken M, Mulvey M, Laupland KB (2007). Molecular epidemiology of CTXM-producing Escherichia coli in the Calgary Health Region: emergence of CTX-M-15-producing isolates. Antimicrob. Agents Chemother. 51: 1281-1286.

Pelczar JR, Harley JP, Klein DA (1993). Microbiology: Concepts and Applications. McGraw-Hill Inc., New York, pp. 591-603.

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Case Report

Recurrent giant malignant peripheral nerve sheath tumor of the scalp with intracranial extension

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Malignant peripheral nerve sheath tumors (MPNSTs) are rare neoplasms, usually arising from somatic soft tissues or peripheral nerves. The incidence of MPNSTs is approximately 0.001% in the general population. MPNSTs are mainly located in the buttocks, thighs, brachial plexus, and paraspinal region. Scalp is an unusual and surgically challenging site of occurrence. We report a case of giant recurrent MPNST in the left fronto-parietal region, with intracranial extension, in a 58 year old female which was excised completely along with the involved overlying skin, and reconstruction was done for the bony and skin defect. She was given adjuvant radiotherapy. She is doing well after treatment and is in regular follow up. MPNST should be considered by neurosurgeons in the differential of an enlarging scalp soft-tissue lesion with bony and intracranial involvement. Scalp MPNSTs are mostly aggressive lesions, and multimodality approaches are necessary to optimize outcomes

Key words: Malignant peripheral nerve sheath tumors (MPNST), scalp, intracranial, surgery.

INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNSTs) are rare neoplasms, usually arising from somatic soft tissues or peripheral nerves. The incidence of MPNSTs is approximately 0.001% in the general population (Al-Gahtamy et al., 2005). MPNSTs are mainly located in the buttocks, thighs, brachial plexus, and paraspinal region (Wanebo et al., 1993). To the best of our knowledge, only 3 cases of MPNSTs of the scalp with intracranial extension have been reported in the English literature (Garg et al., 2004; Ge et al., 2010; Kumar et al., 2007).

We report a case of giant recurrent MPNST in the left fronto-parietal region, with intracranial extension, in a 58 year old female which was excised completely along with the involved overlying skin and bony reconstruction was done for the bony defect.

CASE REPORT

A 58 year old female presented to us with progressive right sided weakness for the past 3 months along with a gradually increasing nodular swelling in the left parietal scalp. The patient was operated 22 years ago for the swelling at the same site with surgical excision, and bony removal and was advised adjuvant radiotherapy which the patient did not undergo. The details of the previous treatment including the biopsy report were not available to us. She remained asymptomatic for all these years till 3 months back when she started having the present problem. On examination, she was conscious, and oriented with normal higher mental functions. There was a right upper motor neuron type facial involvement. She had right hemiparesis with a power of 0/5 in the right upper limb and 2/5 in the right lower limb. Local examination revealed a 3 × 3 cm hard nodular swelling in the left parietal scalp with erythematous and indurated overlying skin, fixed to the underlying mass. There was a 5 × 5 cm sized bony defect in the left fronto-parietal region reaching midline, and previous surgical scar was healthy.

The brain magnetic resonance imaging (MRI) revealed a 7 × 6 × 6 cm sized extraxial lobulated mass lesion in the left fronto-parietal region, hypointense on T1 weighted images and hyperintense on T2 weighted images with

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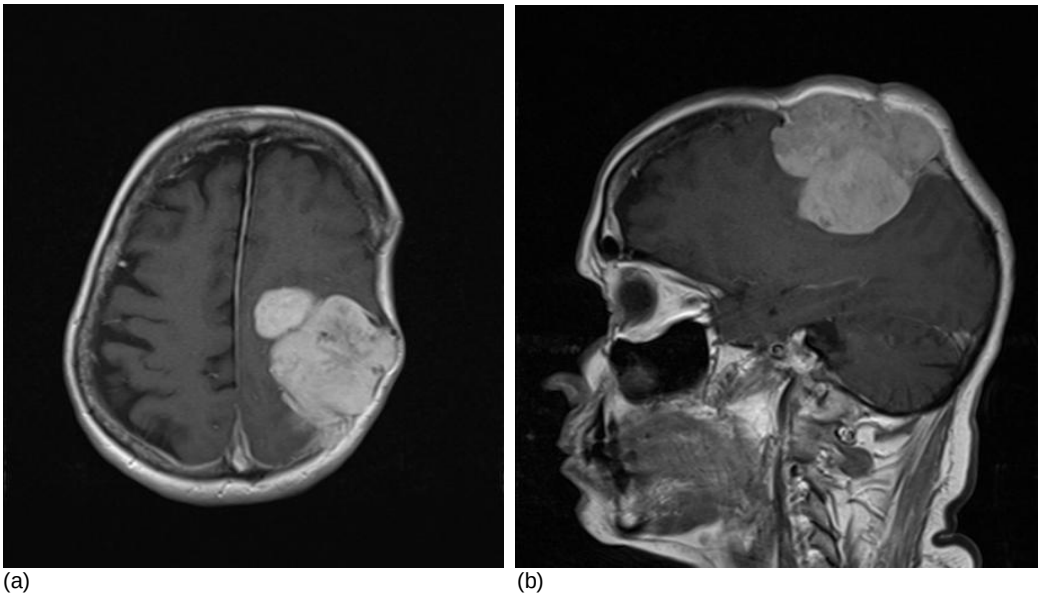

(a) (b)

Figure 1. (a) Preoperative MRI brain contrast enhanced T1 weighted axial image showing a large extra axial lobulated left fronto-parietal mass lesion compression the brain parenchyma with resultant mass effect. (b) Preoperative MRI brain contrast enhanced T1 weighted sagittal image showing a large extra axial lobulated left fronto-parietal mass lesion compression the brain parenchyma with resultant mass effect along with involved overlying skin.

homogenous enhancement on contrast administration, compressing the brain parenchyma and growing out of the bony defect involving the overlying skin (Figure 1; a and b). The patient was investigated for any lesion elsewhere in the body but none was found. The patient underwent exploration via previous scalp incision and complete surgical excision of the lesion, along with removal of overlying involved skin with cranioplasty for bony defect with methylmethacrylate and closure of the scalp defect with transpositioned scalp flap from right fronto-parietal region and split skin grafting.

Post-operative computated tomography (CT) head showed complete excision of the mass (Figure 2). The patient improved neurologically after surgery. The biopsy report showed proliferation of spindle cells with mild pleomorphism in interlacing fascicles, with alternating hypercellular and hypocellular areas (marbelized effect), with cartilaginous metaplasia and buckling of nuclei corresponding to schwannian differentiation. No significant mitoses or necrosis was seen. On immuno-histochemistry, the tumor cells were positive for vimentin and S-100, and negative for EMA, CK, CD34 and SMA, and a final diagnosis of MPNST was established (Figure 3). She was given adjuvant radiotherapy and has been in regular follow up for 2 months and is fine.

DISCUSSION

As defined by the World Health Organization, MPNSTs are malignant tumors arising from a peripheral nerve or showing a nerve sheath differentiation, with the exception of tumors originating from the epineurium or the peripheral nerve vasculature (Kumar et al., 2007). These tumors are treated as a subcategory of soft tissue sarcomas, in which they comprise 3 to 10% of all such tumors (Al-Gahtamy et al., 2005). MPNSTs are associated with genetic alterations such as NF1 loss of heterozygosity.

Approximately one-third of MPNSTs arise *de novo*, whereas the remainder represent a sarcomatous degeneration of a pre-existing plexiform neurofibroma in a neurofibromatosis I or non-neurofibromatosis I patient (World Health Organization, 2000). In present case, as the previous biopsy report was not available, we presume that it was a primary scalp MPNST involving the underlying bone which was excised 22 years ago and which recurred. There were no features of neurofibromatosis I in the present case. MPNSTs usually occur in the third to sixth decades of life and usually affect the medium and larger nerves. Tumor location has been found to be a strong prognostic factor with those in the thoracic and retroperitoneum having worse outcomes (Wanebo et al., 1993). Histopathologically, these are highly cellular tumors that characteristically show a fascicular pattern, spindle-shaped nuclei, and scant cytoplasm. The majority of tumors show geographic necrosis and mitotic activity. Most features were seen in this case, except for mitosis and necrosis.

Magnetic resonance imaging is the investigation of

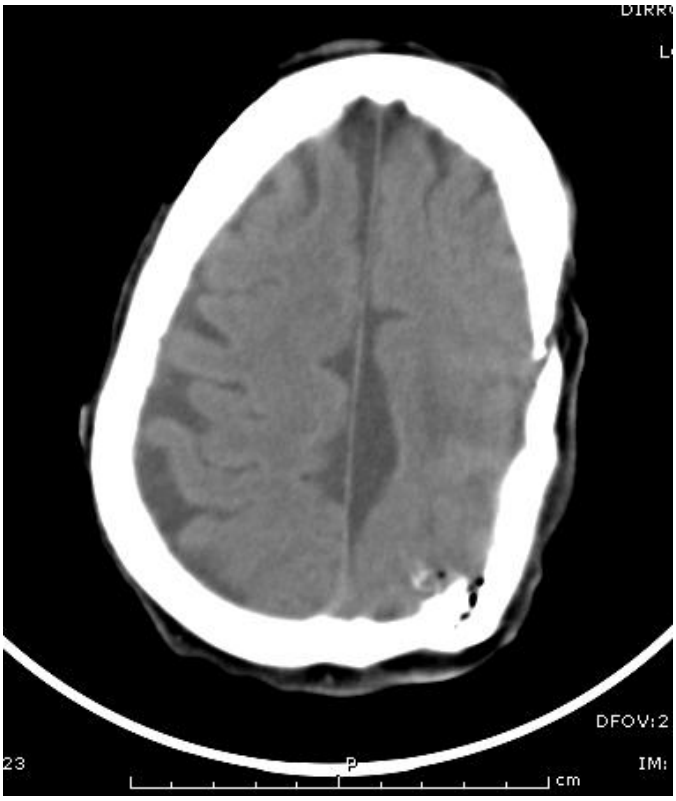

Figure 2. Postoperative contrast enhanced axial CT head image showing complete excision of the tumor and bony reconstruction.

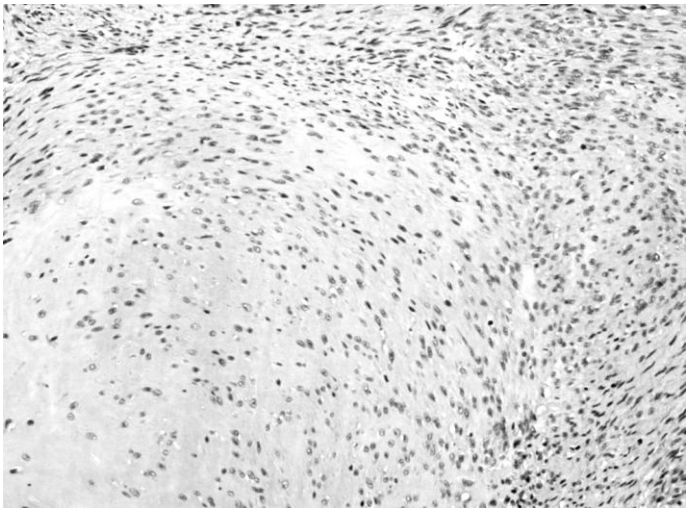

Figure 3. Microphotograph showing interlacing fascicles of spindle cells exhibiting minimal pleomorphism along with buckling of nuclei and cartilaginous metaplasia. (Hematoxylin and eosin, ×100).

choice because it reveals the nerve origin and the relationship to adjacent structures in most cases (Al-Gahtamy et al., 2005). The International Consensus Group has recommended that the current management of MPNST should be identical to that of any other soft tissue tumors. Adjuvant radiation therapy (RT) should be considered for all intermediate- and high-grade lesions, as well as low-grade tumors with positive margins and was given in this case as well (Angelov et al., 1998; Vege et al., 1994). Local recurrences have been reported to vary from 52 to 88.9% for different sites, whereas metastasis (mainly in the lungs and liver) ranged from 11.1 to 18%. The 5-year survival rate among patients with MPNSTs ranges from 30 to 50% (Angelov et al., 1998; Ferner and Gutmann., 2002; Vege et al., 1994). In this case, it recurred locally and there was no metastatic lesion elsewhere in the body.

In view of the high incidence of local recurrence in MPNSTs after surgery, adjuvant postoperative RT has been shown to improve local control. This could be explored further, especially in sites in which complete surgical resection may not always be feasible (for example, the scalp) with intracranial extension (Kumar et al., 2007; Wilson et al., 1994). With MPNSTs being relatively radioresistant, similar to soft tissue sarcomas, an attempt should always be made for near total surgical debulking of the tumors, and adjuvant postoperative RT could help to reduce the local recurrence.

Conclusion

MPNST should be considered by neurosurgeons in the differential of an enlarging scalp soft-tissue lesion with bony and intracranial involvement. Scalp MPNSTs are mostly aggressive lesions, and multimodality approaches are necessary to optimize outcomes

REFERENCES

Al-Gahtamy M, Midha R, Guha A, Jacobs WB (2005). Malignant peripheral nerve tumors, in Beyer MS, Prados MD: Textbook of Neuro-oncology. Elsevier Saunders, Philadelphia. pp. 564–571.

Angelov L, Davis A, O'Sullivan B, Bell R, Guha A (1998). Neurogenic sarcomas: Experience at the University of Toronto. Neurosurgery 43:56–65.

Ferner RE, Gutmann DH (2002). International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis 1. Cancer Res. 62:1573–1577.

Garg A, Gupta V, Gaikwad SB, Mishra NK, Ojha BK, Chugh M, Sharma MC (2004).Scalp malignant peripheral nerve sheath tumor (MPNST) with bony involvement and new bone formation: Case report. Clin Neurol. Neurosurg. 106:340–344.

Ge P, Fu S, Lu L, Zhong Y, Qi B, Luo Y (2010). Diffuse scalp maliognant peripheral nerve sheath tumor with intracranial extension in a patient with neurofibromatosis type 1. J. Clin. Neurosci. 17(11):1443-4.

Kumar P, Jaiswal S, Agrawal T, Verma A, Datta NR (2007). Malignant peripheral nerve sheath tumor of occipital region. Neurosurgery 61(6):1334-5; Discussion E1335.

Wanebo JE, Malik JM, VandenBerg SR, Wanebo HJ, Driesen N, Persing JA (1993). Malignant peripheral nerve sheath tumors. A clinicopathological study of 28 cases. Cancer 71:1247–1253.

WWilson AN, Davis A, Bell RS, O'Sullivan B, Catton C, Madadi F, Kandel R, Fornasier VL (1994). Local control of soft tissue sarcoma of the extremity: The experience of a multidisciplinary sarcoma group

with definite surgery and radiotherapy. Eur. J. Cancer 30:746–751.
World Health Organization (2000). Pathology and Genetics of Tumors of the Nervous System. IARC Press, Lyon. pp. 169–171.
Vege DS, Chinoy RF, Ganesh B, Parikh (1994). Malignant peripheral nerve sheath tumors of the head and neck: A clinicopathological study. J. Surg. Oncol. 55:100–103.

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Full Length Research Paper

Differential behavioral outcome of anxiety tests in runner rats treated with corticosterone

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Both clinical and pre-clinical studies have suggested that physical exercise is beneficial for lowering anxiety. However, some animal studies fail to demonstrate the anxiolytic effect of physical exercise. The inconsistencies among studies may be due to differences in animal models and behavioral tests. Previously, injection of corticosterone (CORT) for 14 days induced depression-like behavior to varying based on was shown. Animal model was used to investigate whether CORT treatment induced anxiety-like behavior and to examine the anxiolytic effect of voluntary running using two behavioral measurements: open field test and elevated plus maze. Results indicated that running reduced anxiety-like behavior in vehicle-treated animals in both tests. Treatment with CORT showed a significant anxiogenic effect in the open field test regardless of the doses, but not in the elevated plus maze. Running reduced anxiety in theopen field test, but showed no effect in elevated plus maze in the CORT-treated rats. The data suggest the discrepancy of these two anxiety-related measures in the animal model of stress.

Key words: Corticosterone (CORT), stress, voluntary running, open field test, elevated plus maze, anxiety-like behavior.

INTRODUCTION

Hippocampus is not only involved in cognitive functions, but also plays an important role in emotional regulation (Mac, 1949) and anxiety state (Bannerman et al., 2004). In our daily life, we always face challenges that are anxiogenic, for example sitting for an examination, job interviews and public presentations. Anxiety is a normal response to a stressor that helps an individual to promptly cope with the demanding situation. Anxiety disorder presents as an excessive pathological form of fear consisting of a fear state with excessive reaction for the actual threat. Anxiety disorder frequently presents in clinical psychiatry with a 30% occurrence rate. In addition, patients with co-occurring symptoms of anxiety always show worsened severity of depression (Mineka et al., 1998).

In animal studies, it has been shown that exposure to acute uncontrollable stressors cause a variety of behaviors called learned helplessness such as exaggerated shock elicited freezing; deficits in shuttle box escape learning. These kinds of stress responses have been suggested to represent the animal analogs of human anxiety (Maier and Watkins, 1998). Physical exercise is known to reduce the signs and symptoms of anxiety disorder and depression with support from a number of human studies (Dun et al., 2001; Merali et al., 2003;

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Blumenthal et al., 2007). Recently, it has been reported that exercise could exert similar anxiolytic effect as antidepressant treatment in animals (Duman et al., 2008). Preventative and curative effects of physical exercise in depression- and anxiety-like behaviors in animal model have also been reported (Binder et al., 2004; Dulawa et al., 2004). In vehicle-treated rats, four or eight weeks of wheel running is able to alter anxiety behavior in the open field test, but not in the elevated plus maze (Burghardt et al., 2004). Chronic running (6-week) reduces anxiety-like behaviors in terms of exaggerated shock-elicited freezing and shuttle box escape deficits in rats exposed to uncontrollable stress (McKinney and Bunney, 1969). However, inconsistent effects of exercise in the animal models of anxiety have also been found in different studies in which animals with voluntary wheel running show anxiolytic effect (Duman et al., 2008; Salam et al., 2009), no effect (Chiang et al., 2010) or anxiogenic effect (Burghardt et al., 2004). The differences in animal models (normal or stressed animals), animal species, and behavioral tests may contribute to the inconsistencies among those studies.

Psychiatric patients suffering from depressive disorders are often associated with hyperactivation of hypothalamus-pituitary-adrenal axis (HPA axis) that leads to elevated plasma corticosteroids. Animal models with repeated stress have been widely used to study the neurobiological changes following stress exposure (Nestler et al., 2002). However, this model may increase the experimental variability since individual differences in the activation of HPA axis in response to stress exposure may result in different levels of CORT elevation among different individuals exposed to the same stressor. The alternative way is to use repeated exogenous CORT administration as a mean to mimic the effect of stress that associated with elevated CORT levels. This model could provide an effective control over the increases in blood CORT levels in the animals and increase depression-like behavior in rats in a dose-dependent manner (Yau et al., 2011b).

However, exogenous administration of CORT has been reported to both increase (Calvo et al., 1998) or decrease (Andreatini and Leite, 1994) the anxiety level in the elevated plus-maze. It is unclear whether the discrepancy is due to dose effect of CORT treatment. It has previously been reported that treatment with different doses of CORT for 14 days produced a graded increase in depression-like behavior and plasma CORT level (Yau et al., 2011b). Furthermore, wheel running or antidepressant treatment could counteract CORT-induced depression-like behavior and depression-impaired memory in the rats. Since there is no experimental data on measuring anxiety-like behavior in animals treated with different doses of CORT, in the present paper, we used different doses of CORT administrations to examine whether there was an increase in anxiety-like behavior in CORT-treated rats; and to characterize the effects of voluntary running on anxiety-related behaviors in the open field test and the elevated plus maze (the two behavioral paradigms that are commonly used in anxiety tests).

In vehicle-treated rats, the results showed that voluntary running reduced anxiety-like behaviors in the open field test and elevated plus maze. In the CORT-treated rats, the anxiety level was significantly increased by CORT treatment and decreased by running in the open field test. However, in the elevated plus maze, neither CORT treatment nor voluntary running affected the anxiety level in the CORT-treated rats. The data may indicate a discrepancy in measuring the anxiety-like behavior between the open field tests and elevated plus maze in the CORT-injected rat model of stress.

MATERIALS AND METHODS

Animal group and treatment

Adult Sprague Dawley (250 ± 20 g, 6 to 7 weeks old) male rats were obtained from the Laboratory Animal Unit, University of Hong Kong. All experimental procedures were approved and followed the guidelines of the Committee on the Use of Live Animals in Teaching and Research, University of Hong Kong. Rats were kept on a 12 h light-dark cycle with *ad libitum* access to food and water. The animals were divided into runner and non-runner groups and were treated with different doses of CORT (30, 40 and 50 mg/kg) or sesame oil for 14 days (n = 8 to 10/group). The day after the CORT treatment (day 15), the rats were subjected to the open field test and elevated plus maze to examine anxiety-like behavior.

Corticosterone (CORT) treatment

CORT (Sigma-Aldrich, USA) at different doses (30, 40 and 50 mg/kg) and sesame oil were prepared and injected subcutaneously according to the method of Hellsten et al. (2002). The dose of 40 mg/kg has been reported to elevete blood levels of CORT over a 24 h period (Sapolsky et al., 1985). A stock of CORT emulsion was prepared by suspending CORT in sesame oil, followed by vortex and sonication. Injection (0.8 ml/ rat) was made subcutaneously in the neck region daily at 4:00 p.m. The CORT treatment was started at the same time when the rats were allowed to run. The control rats received daily injections of sesame oil.

Voluntary wheel running

Runner rats were housed singly in polyethylene cages equipped with running wheels (diameter, 31.8 cm; width, 10 cm; Nalgene Nunc International, NY). Animals were allowed to familiarize with living condition with locked wheels for 3 days prior to the treatment. The locked wheels were then unlocked for 14 days in the runner groups or kept locked for the non-runner groups. Wheel revolutions were recorded by computer using VitalViewer software (Mini Mitter Company, Inc, OR). Non-runners were housed with locked running wheels in cages identical to that of runners.

Open field test

The behavioral test was conducted in a quiet and dimmed room with constant illumination; the test was performed from 2:00 to 4:00 p.m. After 2 h of habituation in the test room, each rat was individually placed into the center of the open field arena (90 × 90

cm with 40 cm-high side walls). The locomotor activity was recorded for 5 min by a video camera. The arena was then cleaned with 70% ethanol and dried with towel for each trial. Results were analyzed using the Smart Junior software (Panlab, Spain). The open field was broken into two zones for analysis: the peripheral and central zones. Anxiety-like behaviors were indicated by the time spent in the peripheral and central areas, while locomotor activity was indicated by average traveling speed and distance over 5 min in the arena.

Elevated plus maze

Each rat was tested in the elevated plus maze 2 h after the open field test in the same room under the same lighting condition. The elevated plus-maze consisted of four arms made of Plexiglas, elevated 50 cm above the floor. Two arms were open (0.5 cm high edges), while the other two arms were enclosed with 36 cm high wall. Each animal was placed onto the center of the apparatus facing an open arm and was then evaluated for 5 min test. The maze was wiped with 70% ethanol and dried between each trial. The behavior was recorded with a video camera and then analyzed using Smart Junior system (Panlab, Spain). Anxiety-like behavior was evaluated through percent time spent in open and closed arms.

Statistical analysis

Two-way analysis of variance (ANOVA) with CORT treatment and running as between-subject factors was performed with Fisher's LSD post-hoc test. A repeated measure ANOVA was applied for analyzing body weight change and running activity over the 14-day treatment period. Student's t-test was only applied for comparison between vehicle-treated non-runners and runners. The statistical difference was determined with P-value < 0.05. Data were presented as mean± standard error of mean (SEM).

RESULTS

Change of body weight and adrenal gland weight

Weight loss of the adrenal gland which occurs after CORT treatment indicates the efficacy of subcutaneous injections of CORT. Repeated measures of ANOVA revealed a significant change in body weight gain during the 14-day treatment period (Figure 1a and b), effect of day: $F_{3,57}$ = 19.2, P = 0.00090). Significant interaction between day and CORT treatment on body weight change was also observed (day X CORT: $F_{3,57}$ = 44.9; P = 0.00053). CORT treatment and running decreased body weight gain during the treatment (effect of CORT: $F_{3,57}$ = 57.2, P = 0.0077; effect of running: $F_{1,57}$ = 7.7, P = 0.00050). The adrenal gland weight was expressed as the ratio of adrenal gland weight to body weight. Two-way ANOVA indicated that the ratio of adrenal gland to body weight was significantly decreased by CORT treatment (effect of CORT: $F_{3,57}$=142.7, P=0.00033) (Figure 1c), but was not affected by running (effect of running, $F_{1,57}$ = 1.1, P = 0.300).

Running activity of CORT-treated runners

Repeated measures ANOVA indicated that all rats increased their running activity during the treatment period (Figure 2: $F_{3,38}$ = 14.8, P = 0.00042). The runners showed increased running activity during the treatment period (effect of day: $F_{3,38}$ = 5.8, P = 0.0060). Runners with CORT treatment showed a relative higher running activity when compared to runners with vehicle treatment; however, there was no significant effect of CORT on increasing running activity (effect of CORT: $F_{3,38}$ = 1.4, P = 0.29).

Running and CORT treatment did not affect locomotor activity in the rats

Results showed that neither CORT treatment nor running for 14 days affected traveling distance (Figure 3a: effect of running: $F_{1,50}$ = 1.0, P = 0.75; effect of CORT: $F_{3,50}$ = 1.8, P = 0.16) and travelling speed (Figure 3b: effect of running: $F_{1,50}$ = 1.4, P = 0.24; effect of CORT: $F_{3,50}$ = 1., P = 0.15) in the open field test. This data suggests that the difference in anxiety-like behavior was not an artifact of altered locomotor activity following CORT treatments.

Anxiety behavior of the CORT-treated runners and non-runners in the open field test

Anxiety-like behavior of the rats was tested in the open field test and elevated plus maze following the 14-day treatment. In the open field test, CORT, nor running showed no significant effect on the time spent in the central area (Figure 3c: effect of CORT: $F_{3,56}$ = 0.8, P = 0.52; effect of running: $F_{1,56}$ = 1.4, P = 0.25). However, there was a relative increase in time spent in the central area in the vehicle-treated runners when compared with the vehicle-treated non-runners (student's t-test, P < 0.05), indicating running reduced anxiety level in the vehicle-treated rats.

Time spent in the peripheral area was increased by CORT (Figure 3d: effect of CORT: $F_{3,47}$ = 3.0, P = 0.042). Post hoc analysis showed that the rats treated with 30 and 40 mg/kg CORT demonstrated a significant increase in time spent in the peripheral area when compared with the vehicle-treated rats (P < 0.05). The main effect of running was also observed (effect of running: $F_{1,47}$ = 16.7, P = 0.00021), indicating running decreased anxiety level in CORT-treated rats in the open field test. There was a significant decrease in time spent in the peripheral area in the vehicle-treated runners when compared with the vehicle-treated non-runners (student's t-test, P < 0.05).

Effect of CORT and running on anxiety-like behavior in elevated plus maze

There was no significant effect of CORT and running on the locomotor behavior in the elevated plus maze (data not shown). Running and CORT treatment was ineffective

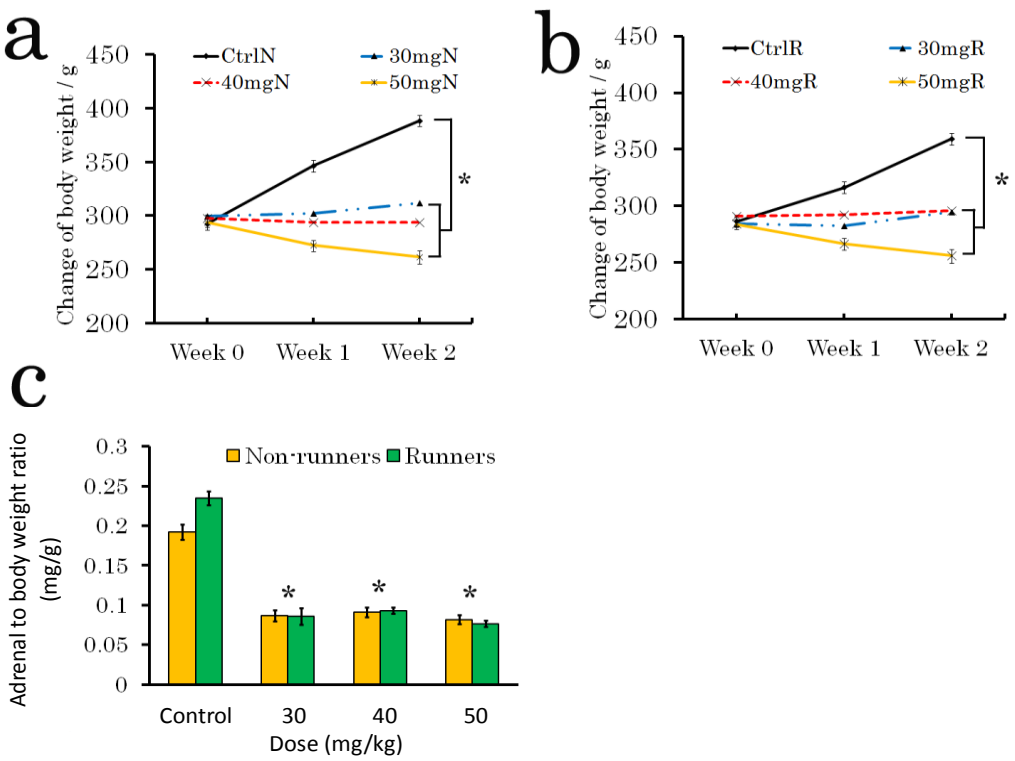

Figure 1. Change of body weight and adrenal weight of the CORT-treated runners and non-runners. (a and b) Body weight gain was significantly decreased by CORT treatments in the non-runners and runners. Running reduced body weight gain. (c) Adrenal to body weight ratio was an indicator for the efficacy of CORT administration. A significantly decreased adrenal weight was found in the CORT-treated rats when compared with the vehicle-treated rats. Ctrl: Vehicle treatment; 30, 40 and 50 mg: doses of CORT per body weight (kg). N: non-runners; R: runners. Value are respresented as mean±SEM. *P < 0.005 compared to the vehicle-treated group.

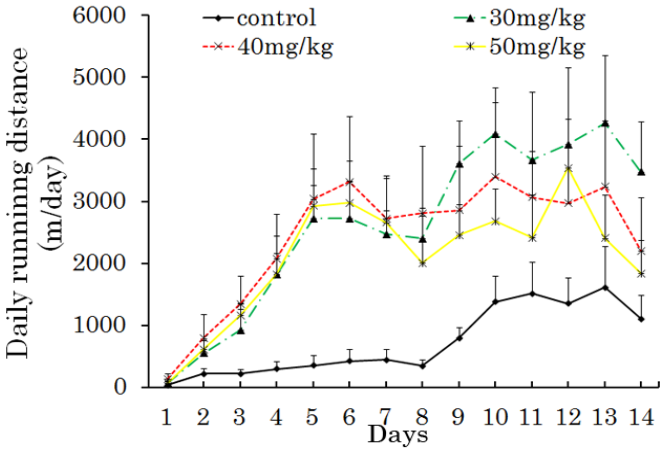

Figure 2. Voluntary running activity of the CORT- and vehicle-treated rats. The running activity was increased in the first week, and was then maintained at the level of 2 to 4 km/day. The rats treated with CORT showed a relatively higher running activity as compared to the vehicle-treated control. Data are expressed as daily mean running distance (m) per day mean ± SEM.

ineffective in altering the time spent in the open arms (Figure 4a: effect of running: $F_{1,51}$ = 0.1, P = 0.71; effect of CORT: $F_{3,51}$ = 0.6, P = 0.63) and in the closed arms (Figure 4b: effect of running: $F_{1,54}$ = 1.5, P = 0.23; effect of CORT: $F_{3,51}$ = 0.4, P = 0.34). The CORT-treated runners and non-runners did not show an increase or decrease in time spent in the open arms and closed arms, indicating that CORT treatment alone or running in CORT-treated rats did not exert effects on anxiety-like behavior in the elevated plus maze. Furthermore, CORT treatment showed no effect on time spent in the center (Figure 4c: effect of CORT: $F_{1,51}$ = 1.11, P = 0.35). Conversely, running showed a main effect on time spent in the center (effect of running: $F_{1,51}$ = 6.06, P = 0.018). Running showed an anxiolytic effect in the vehicle-treated runners as evidenced by relatively decreased percentage of time spent in the closed arms, and increased time spent in the open arms when compared with the vehicle-treated non-runners (student's t-test: P < 0.05).

DISCUSSION

In the present study, we used the open field test and elevated plus maze to examine: (1) whether different doses of repeated CORT treatment could induce anxiety-

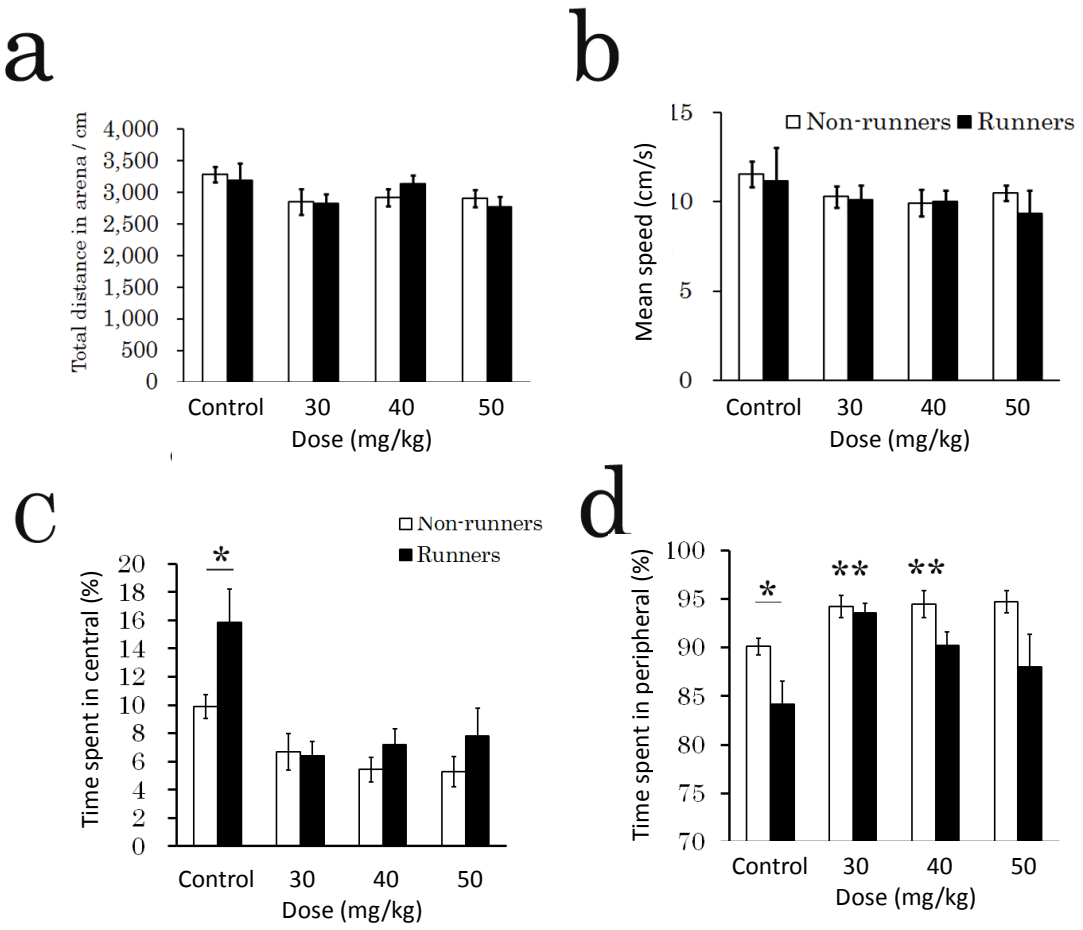

Figure 3. Locomotor activity and anxiety-like behavior of runners and non-runners in the open field test. (a) CORT treatment did not affect locomotor activity in the runners and non-runners. There was no significant difference in the mean speed of the CORT-treated runners and non-runners. (b) Total distance in the arena of the CORT-treated rats remained in the similar level as the vehicle-treated rats. (c) The CORT-treated rats showed no difference in time spent in the central area of the arena when compared with the vehicle-treated rats. However, running significantly increased the time spent in the central area in the vehicle-treated rats, but not the CORT-treated rats. (d) Rats treated with CORT showed increased time spent in the peripheral area. Runners showed a significant decrease in time spent in the peripheral area of the arena when compared to the non-runners. The vehicle-treated runners showed significantly decreased time spent in peripheral areas when compared with the vehicle-treated non-runners. Student's t-test: *P < 0.05 compared to the vehicle-treated non-runners. One-way ANOVA: **P < 0.05 compared to the vehicle-treated rats.

like behaviors; and (2) the counteractive effect of voluntary wheel running on CORT-induced anxiety-like behavior. The vehicle-treated runners showed an increase in time spent in the center of the open field test, in the open arm and the center of the elevated plus maze, respectively.

The findings confirmed that voluntary running for two weeks was associated with a reduced anxiety-like behavior as previously shown in the vehicle-treated rats by other group (Salam et al., 2009). However, CORT treatment increased anxiety level in the open field test, but not in the elevated plus maze. The results raise the question on the discrepancy between these behavioral tests for anxiety-like behavior in animal model of stress.

Although exercise has been shown to reduce anxiety in humans (Dunn et al., 2001; Manger and Motta, 2005) and in exercised animals (Binder et al., 2004), some studies fail to show the anxiolytic effect of exercise (Burghardt et al., 2004; Chiang et al., 2010). Contradictory results on the effects of exercise on anxiety behavior have been reported in some animal studies (Andreatini and Leite, 1994; Calvo et al., 1998). Contradictory results are also found in the open field test and elevated plus maze, for example, same mouse strain was defined as anxious in the elevated plus maze, but non-anxious in the open field test (Trullas and Skolnick, 1993, Rogers et al., 1999). Although these two tests are commonly applied to examine anxiety-like behavior in the animals, the differences in anxiogenic property of these two apparatuses have been reported. Carola et al. (2002) suggested that

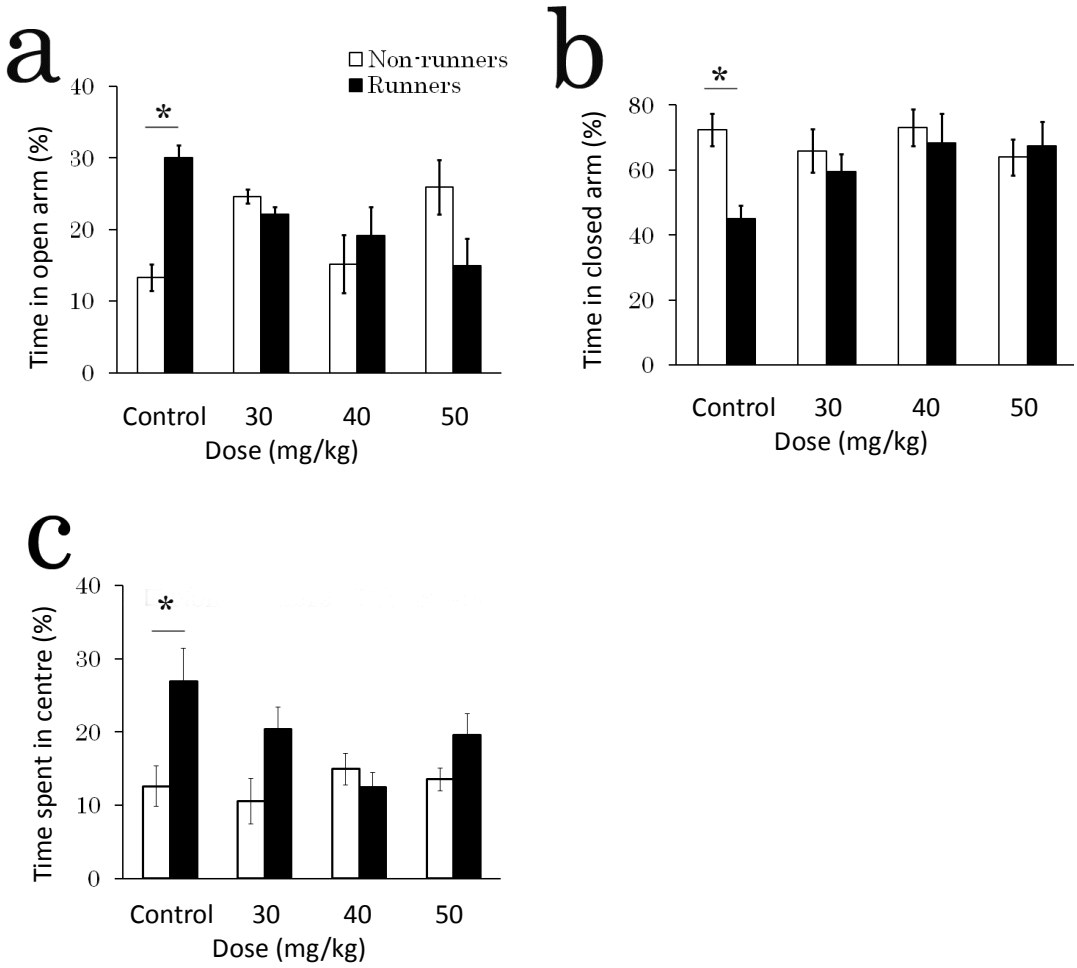

Figure 4. Running decreased anxiety-like behaviour in the vehicle-treated rats, but not CORT-treated rats in the elevated plus maze. Running and CORT treatment did not affect the percentage time spent in the open arms (a) and closed arms (b), respectively. Student's t-test revealed significant increases in time spent in open arms and center (c), and a decrease in time spent in closed arm in the vehicle-treated runners when compared to vehicle-treated non-runners. *P < 0.05 compared to runner counterpart by student's t-test.

discrepancies between these two tests may be due to differences in analyzing criteria among different studies or it is possible that the elevated plus maze may be more anxiogenic to experimental animals than the open field test.

Aversive stress in the open field test is mainly due to the novelty in a new environment, whereas aversive stress in the elevated plus maze is due to novelty and the height of the maze that comprise the behavior of risk assessment during the test, suggesting a stress coping to the animals during the test (Rodgers, 1997). In the elevated plus maze, the animals are placed in the centre of the plus maze as the starting point where animals initially engage in high level of risk assessment, therefore, the design of the elevated plus maze offers more choices and causes a higher level of stress to the animals as compared to the open field test. Nosek et al. (2008) conclude that the differences in the stressfulness between the open field test and elevated plus maze may contribute to the differential outcome. Nosek et al. (2008) suggested that the open field test would be a better measure of passive coping, while the elevated plus maze would be a more sensitive measure of active coping in response to stress.

A consistent result was observed in the vehicle-treated rats that running reduced anxiety level in both the elevated plus maze and open field test. The differential behavioral outcome between these two tests in the CORT-treated rats may suggest a differential stress response between these two tests in our CORT-injected rats. Pre-exposure to the open field test may contribute as a confounding effect since pre-exposure to different novel environment (e.g. the open field) immediately before testing in the elevated plus maze may alter the motor activity in the elevated plus maze and lead to a greater preference of entering the open arms of the maze

(Pellow et al., 1985). However, Walf and Frye (2007) reported that pre-exposure to other testing environment does not alter subsequent behavior of rats and mice in the elevated plus maze. To avoid any possibility of different experience or stressor exposure altering the behavior of rats in the elevated plus maze, the rats were left in the transport cages for 2 h before testing to ensure that the experimental rats have similar level of stress exposure before the behavioral test. Therefore, it is unlikely that the order effect will be a confounding variable to our study. Prut and Belzung (2003) suggested that the open field test is not a valid test for anxiety as it is not sensitive to some effective compounds (e.g. alprozolam and selective serotonin reuptake inhibitor (SSRI)) in treating anxiety disorders, they also concluded that the open field test may be a test for rodent model of normal anxiety.

Increased open field locomotion and decreased anxiety measures following wheel running have been found in the animals after 24 h of wheel running (Dishman et al., 1996; Burghardt et al., 2004). In this study, there was no difference in locomotor activity between the CORT-treated runners and non-runners as indicated by similar activity levels in the open field test and elevated plus maze, though there was a higher running activity in the CORT-treated rats as compared to the vehicle-treated rats.

The presented data shows that CORT treatment significantly increased anxiety-like behavior (increased time spent in peripheral) in the open field test regardless of the doses of CORT treatment, but not in the elevated plus maze. The counteractive effect of running on reducing anxiety-like behavior in CORT-treated rats was only observed in the open field test, but not in elevated plus maze. Gregus et al. (2005) reported that CORT (40 mg/kg) treatment for 21 days in non-running rats significantly increased immobility time in the forced swim test, but showed minimal effect on anxiety-like behavior in the open field test. The hippocampus has been known to play a crucial role in anxiety and depression. The dorsal and ventral hippocampi exhibit discrete functions in regulating learning and emotion, respectively. It has been reported that lesions of dorsal hippocampus led to relatively a weak anxiolytic-like effect, while lesions of ventral hippocampus produced a robust anxiolytic-like effect (Bertoglio et al., 2006; Pentkowski et al., 2006). Recently, it has been suggested that adult neurogenesis in the dorsal and ventral hippocampus might function in a dissociated way (Duncko et al., 2007) in which the dorsal hippocampus is likely specialized for memory functions, whereas the ventral hippocampus is dedicated to anxiety functions (Engin and Treit, 2007). Our previous study showed that physical exercise in terms of running wheel could protect the animals from detrimental effects of CORT via restoring adult neurogenesis and dendritic atrophy in the dorsal part of the hippocampus (Yau et al., 2011a). Several studies reported that a decrease in hippocampal neurogenesis is associated with an increase in anxiety-related behaviors (Ageta et al., 2008; Bergami et al., 2008; Revest et al., 2009). In particular, Revest et al. (2009) demonstrated an increased anxiety-like behavior in transgenic mice with an inducible reduction in neurogenesis throughout the rostro-caudal axis of the dentate gyrus. It is possible that depressive behavior and memory impairment is more dependent on the dorsal part of the hippocampus, while anxiety behavior is more dependent on the ventral part of the hippocampus.

We have previously reported that the dorsal hippocampal neurogenesis was increased in rats with two-week voluntary wheel running (Yau et al., 2011b). This study demonstrated that running decreased anxiety-like behavior in vehicle-treated rats; the promoting effect of running on adult neurogenesis and structural changes in the ventral hippocampus could possibly contribute to the observed effects of wheel running in our vehicle-treated rats. However, this speculation warrants further investigation with examination on the effects of specific blockade of ventral or dorsal hippocampal neurogenesis on emotional behavior.

In summary, these results have demonstrated that voluntary running reduced anxiety-like behaviors in the vehicle-treated rats in two behavioral paradigms: the open field test and the elevated plus maze. The CORT treatment increased anxiety level in the open field test, but showed an effect in the elevated plus maze. Running primarily reduced anxiety-like behavior in the open field test, but not in the elevated plus maze in the CORT-treated rats. The data indicated a differential anxiety-like behavior measured by these two tests in the CORT-treated rats. Extra attention should be given to the discrepancy of these two anxiety-related measures in animal model of stress since the physiological basis of anxiolytic effect of exercise will only be revealed with consistency of effects of exercise across the anxiety-related measures.

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REFERENCES

Ageta H, Murayama A, Migishima R, Kida S, Tsuchida K, Yokoyama M,

Inokuchi K (2008). Activin in the brain modulates anxiety-related behavior and adult neurogenesis. Plos One .3(4):e1869.
Andreatini R, Leite JR (1994). The effect of corticosterone in rats submitted to the elevated plus-maze and to to pentylenetetrazol-induced convulsions. Prog. Neuropsychopharmacol. Biol. Psychiatry 18:1333-1347.
Bannerman DM, Matthews P, Deacon RM, Rawlins JN (2004). Medial septal lesions mimic effects of both selective dorsal and ventral hippocampal lesions. Behav. Neurosci. 118:1033-1041.
Bergami M, Rimondini R, Santi S, Blum R, Gotz M, Canossa M (2008). Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. Proc. Natl. Acad. Sci. USA. 105:15570-15575.
Bertoglio LJ, Joca SR, Guimaraes FS (2006). Further evidence that anxiety and memory are regionally dissociated within the hippocampus. Behav. Brain Res.175:183-188.
Binder E, Droste SK, Ohl F, Reul JM (2004). Regular voluntary exercise reduces anxiety-related behaviour and impulsiveness in mice. Behav. Brain Res. 155:197-206.
Blumenthal JA, Sherwood A, Rogers SD, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, O'Connell C, Johnson JJ, Patidar SM, Waugh R, Hinderliter A (2007). Understanding prognostic benefits of exercise and antidepressant therapy for persons with depression and heart disease: the UPBEAT study--rationale, design, and methodological issues. Clin. Trials 4:548-559.
Burghardt PR, Fulk LJ, Hand GA, Wilson MA (2004). The effects of chronic treadmill and wheel running on behavior in rats. Brain Res. 1019:84-96.
Calvo N, Martijena ID, Molina VA, Volosin M (1998). Metyrapone pretreatment prevents the behavioral and neurochemical sequelae induced by stress. Brain Res. 800:227-235.
Carola V, D'Olimpio F, Brunamonti E, Mangia F, Renzi P (2002). Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice. Behav. Brain Res. 134:49-57.
Dishman RK, Dunn AL, Youngstedt SD, Davis JM, Burgess ML, Wilson SP, Wilson MA (1996). Increased open field locomotion and decreased striatal GABAA binding after activity wheel running. Physiol. Behav. 60:699-705.
Dulawa SC, Holick KA, Gundersen B, Hen R (2004). Effects of chronic fluoxetine in animal models of anxiety and depression. Neuropsychopharmacology 29:1321-1330.
Duman CH, Schlesinger L, Russell DS, Duman RS (2008). Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. Brain Res. 1199:148-158.
Duncko R, Cornwell B, Cui L, Merikangas KR, Grillon C (2007). Acute exposure to stress improves performance in trace eyeblink conditioning and spatial learning tasks in healthy men. Neurobiol. Learn Mem. 14:329-335.
Dunn AL, Trivedi MH, O'Neal HA (2001). Physical activity dose-response effects on outcomes of depression and anxiety. Med. Sci. Sports Exerc. 33:S587-597; discussion 609-510.
Engin E, Treit D (2007). The role of hippocampus in anxiety: intracerebral infusion studies. Behav. Pharmacol. 18:365-374.
Gregus A, Wintink AJ, Davis AC, Kalynchuk LE (2005). Effect of repeated corticosterone injections and restraint stress on anxiety and depression-like behavior in male rats. Behav. Brain Res. 156:105-114.
Hellsten J, Wennstrom M, Mohapel P, Ekdahl CT, Bengzon J, Tingstrom A (2002). Electroconvulsive seizures increase hippocampal neurogenesis after chronic corticosterone treatment. Eur. J. Neurosci.16:283-290.
Mac LP (1949). Psychosomatic disease and the visceral brain; recent developments bearing on the Papez theory of emotion. Psychosom. Med. 11:338-353.
Maier SF, Watkins LR (1998). Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol. Rev. 105:83-107.
Manger TA, Motta RW (2005). The impact of an exercise program on posttraumatic stress disorder, anxiety, and depression. Int. J. Emerg. Ment. Health 7:49-57.
McKinney WT, Jr., Bunney WE, Jr. (1969). Animal model of depression. I. Review of evidence: implications for research. Arch. Gen. Psychiatry 21:240-248.
Merali Z, Levac C, Anisman H (2003). Validation of a simple, ethologically relevant paradigm for assessing anxiety in mice. Biol. Psychiatry 54:552-565.
Mineka S, Watson D, Clark LA (1998). Comorbidity of anxiety and unipolar mood disorders. Annu. Rev. Psychol. 49:377-412.
Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002). Neurobiology of depression. Neuron 34:13-25.
Nosek K, Dennis K, Andrus BM, Ahmadiyeh N, Baum AE, Solberg Woods LC, Redei EE (2008). Context and strain-dependent behavioral response to stress. Behav. Brain Funct. 4:23.
Pellow S, Chopin P, File SE, Briley M (1985). Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci. Methods 14:149-167.
Pentkowski NS, Blanchard DC, Lever C, Litvin Y, Blanchard RJ (2006). Effects of lesions to the dorsal and ventral hippocampus on defensive behaviors in rats. Eur. J. Neurosci. 23:2185-2196.
Prut L, Belzung C (2003). The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. Eur. J. Pharmacol. 463:3-33.
Revest JM, Dupret D, Koehl M, Funk-Reiter C, Grosjean N, Piazza PV, Abrous DN (2009). Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Mol. Psychiatry 14:959-967.
Rodgers RJ (1997). Animal models of 'anxiety': where next? Behav. Pharmacol., 8:477-496; discussion 497-504.
Rogers DC, Jones DN, Nelson PR, Jones CM, Quilter CA, Robinson TL, Hagan JJ (1999). Use of SHIRPA and discriminant analysis to characterise marked differences in the behavioural phenotype of six inbred mouse strains. Behav. Brain Res. 105:207-217.
Salam JN, Fox JH, Detroy EM, Guignon MH, Wohl DF, Falls WA (2009). Voluntary exercise in C57 mice is anxiolytic across several measures of anxiety. Behav. Brain Res. 197:31-40.
Sapolsky RM, Krey LC, McEwen BS (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. J. Neurosci. 5:1222-1227.
Trullas R, Skolnick P (1993). Differences in fear motivated behaviors among inbred mouse strains. Psychopharmacology 111:323-331.
Walf AA, Frye CA (2007). The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. Nat. Protoc. 2:322-328.
Yau SY, Lau BW, So KF (2011a). Adult hippocampal neurogenesis: a possible way how physical exercise counteracts stress. Cell Transplant 20:99-111.
Yau SY, Lau BWM, Tong JB, Ching YP, Lee TMC, So KF (2011b). Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. PlosOne 6:1-15.

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Full Length Research Paper

Psychiatric symptoms and disorders in seizure cases referred to psychiatric out-patient service

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Epilepsy and seizure disorders affect more than 1% adult population. Associated psychiatric problems are reported to increase and worsen the morbidity. In Nepalese context of scant data, this study was conducted to sort-out psychiatric symptomatology and disorders among psychiatry out-patient seizure patients. This hospital-based descriptive study analyzed 100 consecutive seizure patients visiting a psychiatric out-patient service in a 1-year period. Seizure diagnosis was as per clinical evidence and electroencephalography (EEG) findings; psychiatric symptomatology was checked and rated with the help of 'Brief psychiatric rating scale' (BPRS) and psychiatric diagnoses were made according to 'International Classification of Diseases: ICD-10'. In this study, 51% subjects were male. Forty-two patients had family history of significant illness, including seizure in 15% and psychiatric illness in 19%. Forty five percent had ICD-10 diagnosis of 'mental and behavioural disorders' and all, including the ramaining 55% had significant psychopathology. Mood (mainly depression) and anxiety disorders were the most common psychiatric co-morbidities. The most common BPRS items (besides seizure and related) were: somatic, mood, psychotic, hostility and anxiety symptoms. Hence, seizure may manifest with various psychopathology mainly: somatic, mood, psychotic, hostility and anxiety besides seizure-related (for example disorientation and motor) symptoms. A number of psychiatric disorders, mainly depression co-occur in seizure.

Key words: Epilepsy, mental illness, psychiatric symptoms, seizure.

INTRODUCTION

Seizure disorder or epilepsy is one of the most common neuro-psychiatric disorders, affecting about 1% of population within the age of 20 years, and even more in some parts of the world (Hauser and Annegers, 1993). It is one of the largest neuro-psychiatric contributors of Global Burden of Disease by Disability Adjusted Life Year (DALY) (World Bank, 1993). It may be associated with a range of other disorders; those as a causative factor, and effect or manifestation of seizure itself (Mendez, 2009; Raghuthaman et al., 2005; Lishman, 1998; Engel et al., 1986). Depression (Ettinger et al., 2004; Kanner, 2003), anxiety, and psychotic disorders (Nadkarni et al., 2007) are frequently reported higher than among general population (de Araújo Filho et al., 2007). Seizure is associated also with various syndromes, as a manifestation of seizure itself or as induced by seizure, referred to as 'organic mental disorders', for example psychotic, mood, etc (World Health Organization, 1993; American Psychiatric Association, 2000). Profile of those associated disorders and psychopathology offer the insight into common etiological factors in a particular setting and manifest features, leading to better management and prevention strategies.

We have few local data from Nepal about this common but disabling illness, more so about its co-morbid psychiatric disorders and associated symptoms. Hence, we conducted this cross-sectional descriptive study in the Department of Psychiatry, B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal in 2006/2007 to sort-out psychiatric symptomatology and disorders among

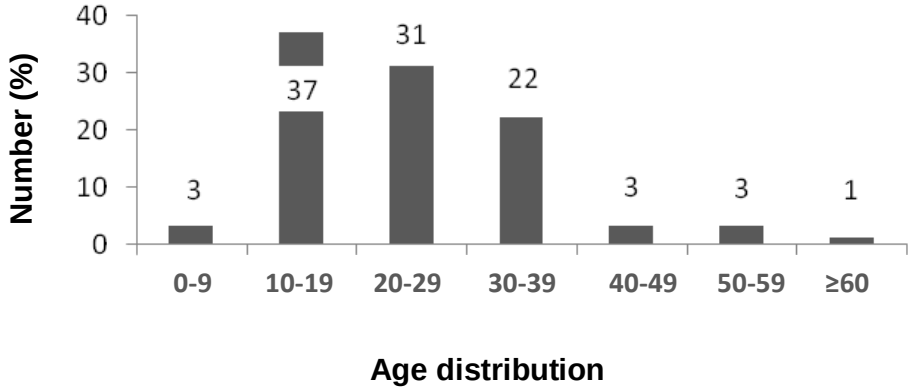

Figure 1. Age distribution.

seizure patients.

MATERIALS AND METHODS

This study, with purposive sampling, enrolled 100 consecutive seizure disorder (SD) patients clinically diagnosed or diagnosed with the help of electroencephalography (EEG), and associated with one or other clinically significant/manifest psychopathology for which they came in contact and consulted with the psychiatrist/investigator in the study period of 1 year duration from August, 2006 to July, 2007. Those patients who did not give consent and were severely medically unstable were excluded.

The number of subjects required that is, sample size was calculated by using the formula: $N = (1.96)^2 \times P \times (100 - P) / [P \times \beta]^2$. Where, N = number of sample, P = estimated prevalence and β = beta error, maximum permissible is 20%; the smaller the figure, the better is the power. We took 50% as the estimated prevalence of psychiatric co-morbidities because we came across the range of 30 to 60% for comorbid psychiatric disorder as a whole in literature (Mendez, 2009; Raghuthaman et al., 2005; Lishman, 1998). The subjects were those who had some psychiatric symptom and had come for psychiatric consultation and also because the objective was to study psychopathology profile too, besides the disorder. Hence, keeping the average for estimated prevalence, P as 50% and β error at 0.2, the calculated sample size was 96, and additional 4% subjects were taken for better representation. Hence, the sample size was taken to be 100. The initial concept was to enroll either minimum of 100 or a sizable number that could be enrolled in 1 year period, whichever would be greater and possible. The estimated sample size could be enrolled in more or less of the stipulated study period.

A brief explanation about the study was given and informed written consent was taken from the subject or significant others. Strict confidentiality of information was maintained. The socio-demographic profile and information about the illness (reason for referral, co-morbid conditions, and psychiatric diagnosis) were recorded on a Performa pre-designed for this study. The detailed psychiatric work-up and necessary investigations were done as per the indication, and their affordability and referrals were made to respective departments. The physical diagnoses were recorded as per the department from or to where the referrals were made. The final psychiatric diagnosis and co-morbidities were made according to the 'International Classification of Diseases-10' (ICD-10) (World Health Organization, 1993).

Psychiatric symptomatology were checked, studied and rated with the help of 'Brief psychiatric rating scales' (BPRS) (Overall and Gorham, 1962). This scale is physician rated and is one of the most researched instruments in psychiatry. The process of rating with this scale takes about 15 to 30 min. Reliability coefficients of 0.56 to 0.87 have been reported (Sajatovic and Ramirez, 2003). The rating scale was utilized in this study as a symptom check-list since it consists of a wide range of psychopathologies. The psychopathologies were rated on 1 to 7 point Likert scale, 1 being absent and 7 being extreme, by asking with patient or family member and by direct observation during the assessment by the investigator.

In this study, the score of 4 that is, moderate or more has been operationally defined as clinically significant for the item to be included as present. Data were entered into computer and analyzed using 'Statistical package for social studies' (SPSS 10) software.

RESULTS

Out of a total of 100 patients, 51 were male (with M: F ratio of almost 1: 1), 42% were married, 56% unmarried and 1% widow(er) and separated each. Average age of the subjects was 24.08 (range: 3, 60) years. Age group (10 to 19 years) constituted the largest proportion of 37%, followed by (20 to 29 years) 31% and (30 to 39 years) 22% (Figure 1). We had subjects of different caste/ethnic groups: 32% Mongol (Rai/ Limbu/ Tamang/ Magar/ Sherpa/ Gurung, etc.), 21% Brahmin, 16% Terai ethnic origin (Mandal, Raya, Jha, Yadav, Shah, Gupta, etc.), 12% Chhetri, 10% dalit/disadvantaged, 6% Newar and 3% Indian. Hindus were the most (78%), followed by Buddhists (12%), Muslims 2%, Christians and Kirat 4% each and 43% came from semi-urban, 29% urban, and 28% rural setting. We also had subjects of diverse professions: students (48%), homemakers (25%), labo-rers (9%), farmers (8%) and others. One fifth (20%) were illiterate and the subjects were relatively better educated

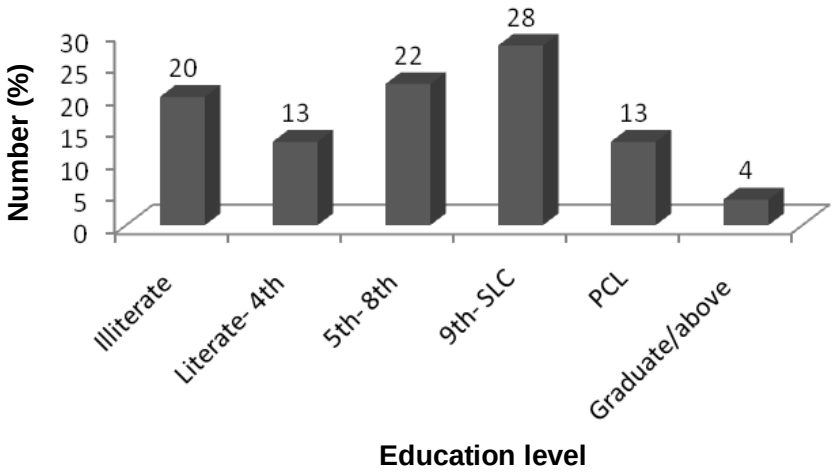

Figure 2. Educational level.

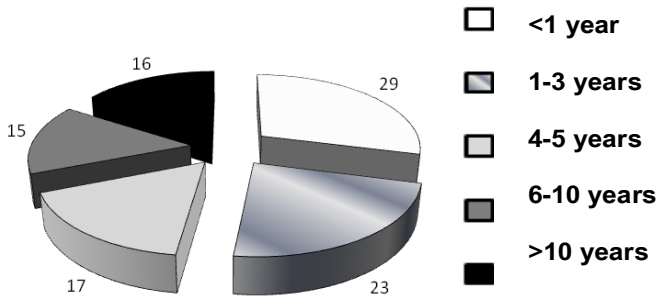

Figure 3. Total duration of seizure illness (%).

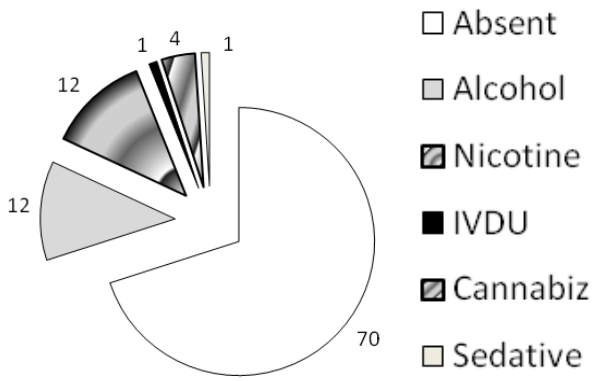

Figure 4. Current psychoactive substance usage (%).

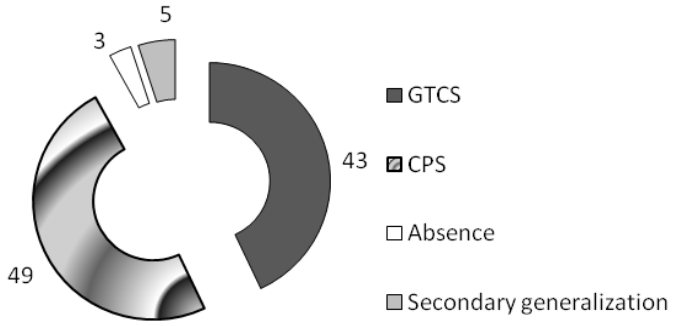

Figure 5. Types of seizure (%).

better educated as a whole (Figure 2).

Most of the cases were brought or accompanied by family member for psychiatric consultation (Table 1). Almost all (96%) had sudden onset and 90% had episodic course of illness. About one third had illness of less than 1 year. More than two-third had seizure morbidity of 1 to 10 years (Figure 3). Nearly half of the total subjects (46%) reported some stressors preceding the seizure attacks. Relational and health related stressors were among the common ones (Table 2). The most common complaints were directly related to seizures, that is misrecognition and or unresponsiveness due to alteration of consciousness (89%). Other main symptoms were somatic or physical complaints (56%) and mood (43%) symptoms (Table 3).

One third of the subjects had a clinically significant illness in their past history, and more than two fifth (42%) had illness in their blood relatives, including 15% with seizure disorder (Table 4). One third (30%) of all seizure patients reported to abuse psycho-active substances (Figure 4). About one fourth of them had some personality traits and 4% had mental retardation which affected the clinical course of illness (Table 5). About half of these seizure subjects had complex partial seizures and 43% generalized tonic clonic seizures (Figure 5).

All subjects had one or other significant BPRS symptom item. Seizure related symptoms: loss of consciousness

Table 1. Sources of referral.

Source of referral	%
Family members	69
Internal Medicine	11
Emergency	4
Family medicine OPD	4
Pediatrics	3
Gynecology/Obstetric	1
Other health centre	1
Alternative medicine	1
Relatives/friends	3
Self	3

OPD: Out-patient department.

Table 2. Types of stressors#.

Stressor type	%
Relational	10
Relative away	4
Death of relative	3
Illness of relative	3
Study related	4
Physical illness/health	10
Environmental	3
Stopping treatment	4
Political/social conflict	8
Sleep disturbance	2

Table 3: Presenting complaints#.

Complaint	%
Misrecognition/ Unresponsive	89
Thought, speech	7
Substance use	3
Behavioral problem	29
Mood symptoms	43
Anxiety	20
Perceptual	16
Somatic/ physical symptoms	56
Self harm	4
Personality changes	3
Others	41
'Aunse purne' (cultural expression)	4

consciousness, abnormal body movements, and stereotypy/mannerism were the most common symptom items among BPRS psychopathology. Other common items were somatic concerns, hallucinatory behavior,

Table 4. Past and family history of illness#.

Illness in past	%
Absent	67
Seizure	9
Neurological	12
Other medical diseases	4
Psychiatric	10
Substance use disorder	1
Not available	2
Illness in family	
Absent	57
Seizure	15
Neurological	8
Other medical diseases	2
Psychiatric	19
Substance use disorder	4

Table 5. Pre-morbid temperament/ traits/ personality.

Personality trait	No. of cases (%)
Well adjusted	64
Cluster 'A'	3
Cluster 'B'	8
Cluster 'C'	12
Others	4
Not applicable	7
Low IQ	4

anxiety, depression and hostility (Table 6). Forty five percent fulfilled the ICD-10 criteria for a psychiatric disorder. The most common psychiatric diagnoses were mood (affective) disorders (23%) and anxiety neurosis (15%). Deliberate self harm was seen in 4%. Out of the total subjects, 55% had some clinically significant psychopathology which did not fulfill criteria for an ICD-10 diagnosis (Table 7). Migraine was the most common physical disease among these seizure cases (Table 8). The most common treatments included antiepileptic drugs. They required some sort of psycho-education, counseling or psychological intervention (Table 9).

DISCUSSION

Seizure disorder, including epilepsy, has the prevalence of about 1% of adult population (Hauser and Annegers, 1993) and is one of the most common and disabling

Table 6. Significant psychological symptoms of BPRS (with scores ≥ 4).

BPRS item	%
Somatic Concern	73
Anxiety	55
Emotional withdrawal	23
Concept disorganization	16
Guilt	8
Tension	39
Mannerism/posturing	69
Grandiosity	19
Depressed mood	42
Hostility	40
Suspiciousness	10
Hallucinatory behavior	56
Motor retardation	29
Uncooperativeness	23
Unusual thought content	8
Blunted affect	9
Excitement	37
Disorientation/derealization	89

Table 7. Psychiatric diagnosis#.

Diagnosis	%
ICD-10 diagnosis present	45
Delirium	1
Substance use (F10-F19)	7
Schizophrenia (F20-29)	4
Mood (affective) (F30-39)	23
Neurotic, Stress, anxiety (F40-49)	15
Mental retardation	4
ADHD	1
Intentional self harm	4
Significant mental symptom only	*55*

Table 8. Co-morbid physical diagnosis#.

Disease	%
Infection/malignancy	3
Thyroid/endocrine	3
Migraine	12
Head injury	2
Cardio-vascular	3
Vertigo	1

Table 9. Management strategies#.

Treatment modality	%
Antipsychotic	15
Benzodiazepines	23
Antidepressant	18
Carbamazepine	49
Sodium valproate	39
Other AED	26
Supplementation	25
Other/IV fluids	8
Counseling/psycho-education/psychological	78

Multiple response category: one respondent may have ≥ 1 responses.

neuro-psychiatric disorders (World Bank, 1993). It is basically the neuro-psychiatric manifestation of paroxysmal hyper-synchronous brain discharges (Mendez, 2009; Raghuthaman et al., 2005; Lishman, 1998). Different seizure or epilepsy types have various clinical features, for example alteration of consciousness (simple or complex) and convulsions (focal or generalized), as comprehensively classified by 'International League against Epilepsies' (1981) (Engel, 2001). Seizure is an important differential diagnosis in cases of episodic phenomena, with a mixture of neurological, somatic and psychiatric symptoms and seizure attack is sometimes precipitated by psycho-social stress, though to a less extent, as most of the mental disorders (Mendez, 2009; Raghuthaman et al., 2005).

Besides the psychiatric manifestations, seizure patients are reported to suffer more from various psychiatric problems than general population. Mood, anxiety and other neurotic (pseudo-seizures or dissociative), psychotic disorders, personality problems, mental retardation and cognitive changes, and suicide and self injurious behaviours are seen more among seizure cases (Mendez, 2009; Raghuthaman et al., 2005; Lishman, 1998). It is however, at times difficult to distinguish them as independent or secondary to seizure activity.

The co-morbid mental illness further worsens the quality of life of the patients. Hence, psychiatric manifesttations and associations in seizures or epilepsies deserve a particular attention. Timely identification and proper proper management will enhance the better productivity and quality of life whereas seizure itself is reported under-diagnosed and under-treated (Eisenberg, 1997). More so because of prevalent myths and misconceptions about psychiatric illness, epileptics hesitate to seek help from mental health professionals even when they are in dire need.

There is a dearth of data about seizure, particularly about its psychiatric manifestations and associations in Nepalese context. We have to rely on our clinical

Observations (Shakya., 2012) and to make assumptions from the data of other parts of world. This study aimed to explore the associated psychopathology and psychiatric co-morbidities in seizure disorders. It was also anticipated that it would open avenues for the studies in other aspects of the disease; like psycho-social, community based prevalence, etiological aspect etc.

This is a hospital based cross sectional descriptive study in 100 consecutive seizure disorder cases, with some psychiatric complaints or symptoms hence, coming in contact with the investigator in the Department of Psychiatry, BPKIHS, Dharan, Nepal during the study period. It utilized the ICD-10 and BPRS as research tools, both being administered by clinician and widely validated across the world (Overall and Gorham, 1962; Sajatovic and Ramirez, 2003). For pre-morbid personality problem, the cluster concept of Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV) (American Psychiatric Association, 2000) was adopted for the sake of simple and comprehensive categorization. As both systems of classification of disorders have similar or equivalent categories to a great extent, this cluster concept would not make much difference.

Majority of the subjects were in the age range of 10 to 39 years. It is on the whole because child and adolescent patients usually visit the Department of Pediatrics and adult patients visit Department of Psychiatry and Internal Medicine in this institute. The 'male: female' ratio being more or less 1:1 is consistent with most of the studies (Hauser and Annegers, 1993; Mendez, 2009; Raghuthaman et al., 2005). Mere 20% illiterate subjects seeking help in this study, obviously less than the general population, reflects the fact that more illiterate people might have been suffering from seizures or epilepsies in community without treatment (Eisenberg, 1997).

Most of the cases in this study were brought by family members when the symptoms did not disappear with other measures, mainly traditional healing, or when they developed additional problems like psychiatric illness. They presented late to medical services; less than one third of the subjects had come to this service within 1 year of the onset of seizure morbidity, reflecting the sad reality about the under-diagnosis (Eisenberg, 1997). Majority had sudden onset and episodic course of illness. Nearly half of the total subjects recall some precipitating stressors for seizure attacks, relational and health related problems being the most common ones.

When they presented to the health service, seizure related symptoms like loss or alteration of consciousness, misrecognition and abnormal body movements (stereotypy/mannerism) were the most common symptom items among the BPRS psychopathology. Other frequent psychopathologies were somatic concerns (headache, body ache, etc), hallucinatory behavior, anxiety, depression and hostility. Though in general population also, depression and anxiety are the most common mental problems (Murray and Lopez, 1996), they are even more among these epileptic subjects. This fact has been replicated in the diagnostic profile of this study too, showing mood and anxiety as being the most common psychiatric co-morbidity, and in the BPRS scoring of associated or manifested psychopathology, showing somatic concerns, hallucinatory behavior, anxiety, depression and hostility as being other most common symptom items with scores 4 or more. Thirty percent re-vealed to use psycho-active substances currently, mainly alcohol and nicotine, which was less than in other general psychiatry patients' profile studies of this institute (Shakya et al., 2009), but clearly in excess to general population (Murray and Lopez, 1996).

One third of the subjects had some significant illness, mainly neuro-psychiatric illness in their past. More than two fifth (42%) of the subjects had family histories of significant illnesses. Fifteen percent of the subjects had some blood relatives with seizure which is similar to Western data (Mendez, 2009; Lishman, 1998).

In this hospital based study conducted in general psychiatry service setting, partial seizure (mainly complex) was the most common seizure type (49%), followed by generalized tonic clonic seizures (GTCS 43%). This is consistent with the fact about the prevalence of seizure types in adult population (Mendez, 2009; Raghuthaman et al., 2005). About one third had some personality traits significant enough to affect the clinical course of illness. People of all clusters were affected by seizures, though Cluster C traits were the most common. Mental retardation was present in 4 cases.

In seizure and epilepsy patients coming to this psychiatric service, 45% had psychiatric co-morbidities (ICD-10 diagnosis), mood and other neurotic/anxiety disorders being the most common as in Western/other studies (Mendez, 2009; Raghuthaman et al., 2005) and the remaining 55% had some significant mental symptoms, with the BPRS score 4 (moderate) or more but did not fulfill the ICD-10 criteria for any psychiatric disorder.

Suicide phenomena are relatively more in these seizure patients than in general population (Thapa and Carlough, 2000). The high rate may be because of the high co-morbidity and severe grading of psychopathology at the time of presentation. The suicide problem in this region needs validation with further community based studies.

As in other parts of the world, the Nepalese clinicians rely on various antiepileptic drugs like Carbamazepine, Sodium valproate and other anti-epileptic drugs. High psychiatric symptoms and co-morbidities were additional consideration during management of these cases; many of them needed benzodiazepines, anti-psychotics and antidepressants. Carbamazepine and Sodium valproate were over representing in this study, maybe because they were considered also for their mood stabilizing and other favorable effects besides antiepileptic property. Some

forms of psychological interventions are complimentary to drug therapy, for example psycho-education.

Our study is biased in a way since it enrolled only those patients who had some manifest mental symptoms and came in contact with the investigator in Department of Psychiatry. Hence, this may not reveal the true prevalence rate but we believe that this study satisfactorily depicts the range of possible psychopathology and psychiatric disorders associated with seizure disorders and looking at the cause and effect relationship of psychiatric symptom/disorder and seizure is beyond the objective/scope of current study which might be the topic for further research here. These observations however corroborate that psychiatric affliction, association, manifestation or co-morbidity is common in seizure disorders and epilepsies from different standpoints: etiological, clinical manifestations, co-morbidities and management. Hence, collaboration among various departments is crucial and it increases the success rate of treatment. The seizure patients should also be aware about these facts and should not hesitate to seek psychiatric help when needed.

Conclusions

1. Seizure and epilepsy patients usually present late (after 1 year of seizure) to the psychiatric service when they also have other co-morbidity, other traditional measures do not work, they are severely affected (high BPRS scores) and have to be brought by family members.
2. Some of them have past history of illness, including neuro-psychiatric illness. Many of them have family history of illness, including some with seizure disorder or epilepsy.
3. These seizure patients present with various symptoms such as altered consciousness, stereotypy, other somatic complaints, anxiety, hallucinatory behavior, mood symptoms, etc.
4. Some of them use substances, including alcohol and nicotine, and also have some significant personality traits, mainly of cluster ‘C’. A remarkable proportion of seizure patients presenting with some psychiatric symptoms fulfill the criteria for psychiatric disorders. Others with symptoms also have clinically significant ones. The most common psychiatric diagnosis was mood (affective) disorders, followed by neurotic, stress related and anxiety. A terrific number of them displayed deliberate self harm. Hence, seizure disorders have a wide range of psychiatric association as manifestation or co-morbidity.

REFERENCES

American Psychiatric Association (2000). Diagnostic and Statistical manual of Mental Disorders. 4th ed. Text rev. Washington, DC.

Commission on Classification and Terminology of the International League against Epilepsy (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22:489-501.

de Araújo Filho GM, Pascalicchio TF, da Silva Sousa PC, Lin K, Ferreira Guilhoto LM, Yacubian EM (2007). Psychiatric disorders in juvenile myoclonic epilepsy: a controlled study of 100 patients. Epilepsy Behav. 10(3):437-441.

Eisenberg L (1997). Socio-cultural perspectives. In: Engel J, Pedley TA (Eds.), Epilepsy: A comprehensive textbook. Lippincott-Raven Publishing, New York. pp. 41-6.

Engel J Jr. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 42:796-803.

Engel J Jr., Caldecott-Hazard S, Bandler R (1986). Neurobiology of behavior: anatomic and physiological implications related to epilepsy. Epilepsia 27(2):3-13.

Ettinger A, Reed M, Cramer J (2004). Epilepsy Impact Group. Depression comorbidity in community-based patients with epilepsy or asthma. Neurology 63:1008-1014.

Hauser WA, Annegers JF (1993). Epidemiology of epilepsy and unprovoked seizures in Rochester, Minnesota, 1935-1984. Epilepsia 34:453.

Kanner AM (2003). Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms and treatment. Biol. Psychiatry 54:388-398. Abstract.

Lishman WA (1998). Epilepsy. In: Organic Psychiatry, 3rd ed. Blackwell Science. pp. 237-98.

Mendez MF (2009). Neuropsychiatric Aspects of Epilepsy. In: Sadock BJ, Sadock VA, Ruiz P (eds), Comprehensive Text Book of Psychiatry, 9th ed. Wolters Kluber/ Lippincott Williams & Wilkins, Philadelphia. pp. 451-62.

Murray CL, Lopez AD (1996). The Global Burden of Disease: a Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected. Harvard University Press, Cambridge, Massachusetts.

Nadkarni S, Arnedo V, Devinsky O (2007). Psychosis in epilepsy patients. Epilepsia 48(9)17-9.

Overall JE, Gorham DR (1962). The Brief Psychiatric Rating Scale (BPRS). Psychol. Rep. 10:799-812.

Raghuthaman G, Jacob KS, Ranjith G (2005). Psychiatric aspects of epilepsy. In: Bhugra D, Ranjith G, Patel V (eds.), Handbook of Psychiatry- A South Asian Perspective. Byword Viva Publishers Pvt. Ltd. pp. 117-26.

Sajatovic M, Ramirez LF (2003). Brief Psychiatric Rating Scale (BPRS). In: Rating Scales in Mental Health. Panther Publishers Pvt Ltd, Bangalore. pp.130-33.

Shakya DR (2012). Depression in Seizure disorder- a case report. Health Renaiss. 10(1):59-61.

Shakya DR, Pandey AK, Shyangwa PM, Shakya R (2009). Psychiatric morbidity profiles of referred Psychiatry OPD patients in a general hospital. Indian Med. J. 103(12):407- 411.

Thapa B, Carlough MC (2000). Suicide incidence in the Lalitpur district of Central Nepal. Trop Doct. 30 (4):200-3.

The World Bank (1993). World development report- Investing in health (world development indicators). World Bank and Oxford University Press.

World Health Organization (1993). The ICD-10 Classification of Mental and Behavioral Disorders- Diagnostic Criteria for Research. WHO, Geneva.

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