INTRODUCTION: A variety of psychiatric symptoms are associated with brain tumours. The frequency of the association between brain tumours and behavioural disturbances depends significantly on the location of the tumour. Making the relationship between brain tumours and secondary behavioural changes is becoming more difficult due to the complications of various therapeutic interventions like extensive surgical resection of the tumour mass. We report a case of a rare variant of low grade glioma - protoplasmic astrocytoma, in the left frontal region presenting with various neuro psychiatric manifestations, particularly with neuro cognitive deficits and depression after surgical resection of the tumour. THE CASE. A 33yr old male, graduate, unmarried working in a private company had atypical depressive symptoms for about one year followed by focal seizures. He was later diagnosed to be having left frontal diffusely infiltrating protoplasmic astrocytoma grade II and surgical resection was done. Following surgery he had recurrent episodes of depression along with psychotic features and had weakness over right upper and lower limbs. He also had persistent anxiety symptoms and occasional aggressive outbursts. He was followed up for a period of two years during which he had three depressive episodes. Initially he was responding well to medications and later in the due course, he was becoming treatment resistant. He had severe neurocognitive deficits in the areas of attention, working memory and executive functioning assessed by various neuropsychological tests periodically. His cognitive deficits led to severe work impairment and loss of job.

CONCLUSION. This case illustrates that brain tumour can present with atypical psychiatric manifestations alone during the earlier stages. Surgical removal of the tumour with extensive debulking and causing disruption of various anatomical circuits can lead to severe psychiatric and cognitive disturbances. So a neurosurgical removal should be carefully considered when there is no evidence of malignancy or significant mass effect. In cases in which surgery causes disruption of anatomy, pharmacotherapy is usually warranted. But more frequent treatment failures is common in such cases and treating such cases becomes a real clinical challenge.

Keyword : protoplasmic astrocytoma, post resection, psychiatric sequelaeif !msol>
He was not interested in going to work and became angry for trivial reasons with his family members. He avoided talking with his friends, previously he would enjoy going outing along with his friends every weekend. He was sleepy during morning in office and his sleep was disturbed at night. He started thinking that he had wasted his life by working in courier company and his future is going to be questionable. He didn’t go for work regularly and remained in home most of the day. He started lamenting and had occasional crying spells. His food intake and self-care were reduced. He would sit idle at one place for hours together and would not talk to anyone. He was not taken for any treatment. There was no significant family history suggestive of psychiatric illness in first degree relatives and there were no deviant premorbid personality traits. There was no history of any substance abuse. One year after the onset of these symptoms he had an episode of seizure involving right upper and lower limb associated with loss of consciousness. There was no incontinence and the episode lasted for about two minutes. Then he had repeated episodes of seizures occurring twice a week over a period of 3 months. He was treated by General practitioner but his seizure episodes increased in frequency. He was then referred to neurologist. CT brain was done which showed focal area of hypo attenuation in left frontal region not showing enhancement with contrast. As CT report was inconclusive MRI brain was done and T2-weighted sequences showed diffusely infiltrating lesions with high signal intensity over the left fronto parietal area with slight mass effect. On T1 sequences well defined non enhancing lesion of low-signal intensity with a diameter of about 2.5cm without mass effect suggesting glioma? gangliocytoma. There is no contrast enhancement of this lesion. He was referred to neurosurgeon. The patient and family members were explained about the diagnosis and prognosis and about the immediate necessity of surgical intervention and risks and outcomes of surgery. Left frontal trephine craniotomy and excision of SOL was done. Post-operative CT showed craniotomy defect with bone flap seen in left fronto parietal bone. Left high frontal lobe volume loss noted with high hypo dense areas, air packets and surrounding minimal contrast enhancement. Histo pathological report showed diffusely infiltrating Protoplasmic Astrocytoma Grade II. He was hospitalized for 3 months after surgery and was given 29 sessions Radiotherapy over 2 months. Post operatively he had weakness of right upper and lower limb. He was also put on anticonvulsants Tab. Phenytoin 100mg B.D and Tab. Phenobarbitone 30mg H.S prophylactically. During the Hospital stay he was much distressed about his weakness. 3 months following surgery he become much irritable, started using filthy language and was disturbing other patients in ward. He assaulted his brother telling that he is responsible for all the problems happened to him. He developed suspicious ideas against family members and hospital staff and was referred for psychiatrist opinion and further management of behavioural disturbance. On admission his neurological examination revealed deviation of angle of mouth towards left side, with power of the right upper and lower limbs 3/5 and 4/5 respectively. Deep Tendon reflexes were exaggerated and plantar was extensor over the right side. Pupils were equally reacting and fundus was normal. Mental status examination showed , gaze contact was not maintained and rapport was difficult to establish with reduced psychomotor activity, Speech quantum tone and rate was decreased, reaction time was prolonged, Ideas of hopelessness, worthlessness suicidal Ideas, delusions of persecution against family members, ideas of reference, Second person auditory hallucinations and apathetic mood. Attention was ill sustained and orientation to time place and person was intact. Immediate and recent memory is impaired, remote memory was intact. General fund of information was adequate , he had difficulty in doing two step calculations, Abstract thinking was impaired, Personal Judgement is impaired and insight was grade 3. Lobar function tests were performed and detailed Neuropsychological assessment was done.

The following rating scales were administered. 1.Hamilton Rating scale for Depression1 (HAM-D) 2.Montgomery Asberg Depression Rating Scale2 (MADRS) 3.Brief Psychiatric Rating Scale3 (BPRS) Mini Mental State Examination (MMSE)4 was also administered. Results of neuropsychological tests and rating scales are summarized below.

He made two suicidal attempts and had suspicious ideas and auditory hallucinations. He told that he is going to die of the tumour soon. He was again admitted and treated with Tab. Escitalopram 10 mg O.D., Tab. Haloperidol 1.5mg B.D and Tab. clonazepam 0.5 mg H.S.. He showed only minimal improvement after 3 weeks. Neuropsychological assessment was again done which showed more impairment than the previous time. Some of the symptoms like depressed mood and irritability continued. Dosages were increased ,combination and augmentation were tried but there was poor response. He was evaluated for Electro Convulsive Therapy but ECT was not given as the patient and relatives were not willing for ECT. Frontal Assessment Battery5 (FAB) scoring was made and the results are tabulated in the previous page(Table 3)
He had poor scores on Wechsler’s adult intelligence scale. HAMD score was 34. He was presented in the clinical society meeting and a diagnosis of organic depressive disorder (F06.32) was made. The differential diagnosis given were organic personality disorder and Severe depressive episode with psychotic symptoms (Reactive depression). He was started on Tab. Sertraline 50 mg B.D, Tab. Olanzapine 5mg H.S., and Tab. lorazepam 2 mg. He showed improvement after 2 weeks and his HAMD a score after 2 weeks was 23.

He was given supportive psychotherapy and his family was educated about the course and outcome of illness and the importance of social support.

He was discharged and was followed up for 2 years. He was continuing the same medications. He went for the same job and continued for about 6 months. He was not able to tally the daily accounts and made many mistakes. As he had weakness of his right upper limb he had difficulty in writing and after 6 months he lost the job. 2 months after that he again had a depressive episode. This time the episode was triggered by his job loss. He was again admitted and treated with same medications. Psychometry and neuropsychological assessment was done. His impairment on executive functioning remained the same. MRI revealed no recurrence of tumour tissue.

His anticonvulsant medications were stopped as per the neurologist’s opinion. He was discharged after 10 days. HAMD score was 23. He was given supportive psychotherapy and his family was educated about the course and outcome of illness and the importance of social support.

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13 Depending on the affected hemisphere and the location within the active in working memory tasks. 15-17 The dorsolateral prefrontal lesion in the frontal lobes can result in abnormal behaviours 12, but they are seen more regularly and more strikingly occurring after the frontal lobes. These are not unique to the frontal lobe pathology, certain clinical features have long been associated with damage to the orbitofrontal cortex these symptoms were not present. But the explosive antisocial traits associated with orbitofrontal lesions have been postulated to result from a loss of inhibitory control over the amygdala. 23-25

DISCUSSION

Certain clinical features have long been associated with damage to the frontal lobes. These are not unique to the frontal lobe pathology, but they are seen more regularly and more strikingly occurring after frontal lobe damage than damage to other cortical structures. 13, 19 Depending on the affected hemisphere and the location within the hemisphere, human frontal lobe lesions can result in alterations in attention, insight, mood, planning, and interpersonal communication and causes changes that are often permanent. 13

In each hemisphere, the bulk of the non-motor frontal lobe comprises of prefrontal cortex which is subdivided in to dorsolateral, orbitofrontal, and ventromedial cortices and the anterior cingulate cortex. Prefrontal cortex plays an essential role in integrating impulses from various sensory and limbic circuits for the purpose of generating goal-directed behaviour. 13 This brain region is also active in working memory tasks. 13-17 The dorsolateral prefrontal cortex also supports the regulation of behaviour and control of responses to environmental stimuli. Thus, major features of dorsolateral lesions include decreased executive function and affective disturbance like depression. 14, 18-20

Our patient’s part of the dorso lateral cortex was removed during the surgery as it was mostly comprising the tumor mass. His decreased performance at workplace before surgery was more directly related to the tumour’s effects on the prefrontal areas. 13, 19, 21 Intact orbitofrontal cortices are required for normal judgment and socialization. Patients with orbitofrontal lesions tend to be disinhibited. 16 Unlike dorsolateral lesions, orbitofrontal lesions generally spare cognitive abilities and volition, but they can significantly contribute to the genesis of antisocial behaviours. Indeed, the outbursts, mood fluctuations, self-mutilation, and splitting behaviours seen in borderline personalities may be related to a hypo functioning orbitofrontal cortex. 21, 22 Neuro anatomically, the explosive antisocial traits associated with orbitofrontal lesions have been postulated to result from a loss of inhibitory control over the amygdala. 23-25

Although our patient exhibited some behaviour like aggressive outbursts, there are no mood fluctuations or disinhibited behaviour or self-mutilating behaviour. As his tumour was not located within the orbitofrontal cortex these symptoms were not present. But the presence of uncontrollable aggressive outbursts might be explained due to gliotic changes that have occurred in the mass defect after resection that might have pulled the white matter tracts connecting the orbitofrontal cortex with the other frontal cortical areas. Another possible explanation is a possibility of epileptic focus in the gliotic area.

Ventromedial prefrontal cortex is responsible for the regulation of empathy, foresight and reversal learning. The ventromedial prefrontal cortex has reciprocal connections with the brain regions associated with emotional processing (amygdala), memory (hippocampus) and higher order sensory processing (temporal visual association areas), as well as with dorsolateral prefrontal cortex. In our patient ventromedial cortex is not involved.

The anterior cingulate cortex borders the genu of the corpus callosum and merges into the posterior cingulate. Functionally, the anterior cingulate can be divided into two regions, a rostral affective division and a caudal cognitive division. Connecting these areas is the cingulum, a fibre tract embedded within the anterior cingulate gyrus and terminating in more rostral prefrontal cortices. Functionally, the anterior cingulate may underlie drive (motivated attention) and concentration (attention allocation). 20, 26 Anterior cingulate lesions interfere with these functions, whereas anterior cingulate hyperactivity has been described in most anxiety disorders.

In our patient the presence of predominant anxiety and hyper-arousal symptoms could be explained by the fact that during surgical debulking of the tumour parts of normal brain tissue including connection bundles would have been involved. As our patient had diffusely infiltrative Protoplasmic astrocytoma extensive de bulking was done to remove the entire mass with adhesive infiltrations. The shear and traction forces applied during surgery will have an effect on the integrity of white matter tracts and surgical working over the tumour was nearer to anterior cingulate cortex and cingulum bundle.

Frontal lobe lesions exhibit lateralization with respect to psychiatric or behavioural disturbances. Left hemisphere lesions are more likely to be associated with depression, particularly if the lesion involves the dorsolateral portion of prefrontal cortex. By contrast, right hemisphere lesions are associated with impulsivity and manic behaviours. 26, 31.

Our patient’s tumour was located in the left frontal lobe, and his symptoms were consistent with it. Neuropsychology of executive function: An enormous range of cognitive functions has been attributed to the frontal lobes. These include the initiation of responses, the maintenance of responses, the suppression of irrelevant or inappropriate responses, the planning and organisation of behaviour, abstract and conceptual thinking, monitoring and editing of responses, the temporal organisation of behaviour and memory, aspects of working memory, and the encoding and/or retrieval of new or remote episodic memories. A wide range of tests have been developed to measure some aspect of executive function. Commonly employed are FAS verbal fluency, the Wisconsin card-sorting tests, cognitive estimates, trail making, various tasks that require alternating patterns of behaviour or shifts in response, the Stroop test, working memory or continuous performance tests, prospective memory and source or temporal context memory tasks.

Wisconsin card sorting test: There is clear evidence that impairment was closely related to lesions of the frontal lobes of either hemisphere, with no comparable effects from lesions in other areas of brain. The impairment was chiefly seen with lesions of dorsolateral convexities of the frontal lobe, rather than with inferior and orbital lesions. Moreover, the errors in patients with frontal lobe lesions were chiefly of the perseverative type. Certain qualitative differences were found between the nature of errors with left and right frontal lesions, the former producing the greater overall impairment.

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Forecasting neuropsychiatric symptoms after neuro surgery for tumour removal is difficult because differences in tumour size, differences in surgical technique. Susceptibilities of different brain regions to operative trauma have left patients like ours with a worsening clinical course, such as postoperative psychosis, anxiety symptoms along with severe depression. The prognosis is worse when bulky tumours destroy a larger volume of the brain parenchyma, fundamentally altering the neuroanatomical substrates of behaviour.

Pharmacological management of psychiatric illnesses is the mainstay in modern psychiatry, but this case shows that medication failures may occur in the setting of an underlying brain tumour.

CONCLUSION
This case illustrates that brain tumours can present only with atypical psychiatric manifestations during earlier stages before overt neurological symptoms occur. Understanding of regional frontal lobe functions pertaining to behaviour, cognition, and mood may be helpful to use clinical observations to deduce the location of a putative frontal lobe mass. Dorsolateral frontal lobe lesions affect executive functions, mood and volition. Anterior cingulate lesions influence awareness, concentration, error detection, and affect-mood congruence and causes anxiety symptoms. This case emphasizes that removal of frontal lobe masses cause severe psychiatric disturbances. So a neurosurgical removal should be carefully considered when there is no evidence of malignancy or significant mass effect. In cases in which surgery causes disruption of anatomy, pharmacotherapy is usually warranted. But more frequent treatment failures is common in such cases and treating such cases becomes a real clinical challenge.

References: