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Meningioma and psychiatric symptoms: An individual patient data analysis

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ABSTRACT

Meningioma is a slow-growing benign tumor arising from meninges and is usually asymptomatic. Though neuropsychiatric symptoms are common in patients with brain tumors, they often can be the only manifestation in cases of meningioma. Meningiomas might present with mood symptoms, psychosis, memory disturbances, personality changes, anxiety, or anorexia nervosa. The diagnosis of meningioma could be delayed where only psychiatric symptoms are seen. A comprehensive review of the literature and individual patient data analysis was conducted, which included all case reports, and case series on meningioma and psychiatric symptoms till September 2018 with the search terms "meningioma" and "psychiatric symptoms/ depression/ bipolar disorder/ mania/ psychosis/ obsessive-compulsive disorder". Search engines used included PubMed, MEDLINE, PsycINFO, Cochrane database and Google Scholar. Studies reported varied psychiatric symptoms in cases with meningioma of differing tumor site, size and lateralization. Factors which led to a neuroimaging work-up included the occurrence of sudden new or atypical psychiatric symptoms, a lack of response to typical line of treatment and the presence of neurological signs or symptoms such as headache, seizures, diplopia, urinary incontinence etc. This review emphasizes on the need of neurological examination and neuroimaging in the patients presenting to psychiatry especially with atypical symptoms.

1. Introduction

A brain tumor is a mass or growth of abnormal cells which might present with wide range of symptoms (Crocetti et al., 2012; Ostrom et al., 2015). They are classified based on their histopathologic characteristics or anatomical location. If the origin of the tumor is within the brain tissue, they are called primary brain tumors and if they metastasize to the brain from tumors of other parts of the body, they are called secondary brain tumors. The primary brain tumors originating from glial cells are called gliomas (Davies and Clarke, 2004). Gliomas are of several types such as astrocytomas, oligodendrogliomas, and ependymomas. The brain tumors that are not from glial tissue include meningiomas, schwannomas, cranio-pharyngiomas, germ cell tumors, pituitary adenomas and pineal region tumors. The incidence of brain metastases or secondary brain tumors is estimated to be 10 times more common than the primary brain tumors (Arvold et al., 2016). Brain tumors can present with focal neurological symptoms, seizures, headache, cognitive or behavioral impairment (McFaline-Figueroa and Lee, 2018). Psychiatric symptoms and behavioral manifestations in patients with brain tumors are more common in secondary brain tumors (McFaline-Figueroa and Lee, 2018). The evidence suggests there is increase in prevalence of psychiatric symptoms in patients with brain tumors. The necropsies performed on patients who died in a mental hospital in South Africa during a three year period from 1970 to 1973 found that 27 patients out of 200 had an intra-cranial space-occupying mass (Cole, 1978). This could mean that most of the space occupying lesion in patients who present primarily with psychiatric symptoms remain undiagnosed. In another study, the rate of primary brain tumors in hospitalized psychiatric patients was one in 1,000, which was 20 times more frequent than in the normal population (Kocher et al., 1984).

Meningioma is the most common type of primary central nervous system tumor (Wiemels et al., 2010) presenting as a benign encapsulated solitary intracranial neoplasm in the skull base or over the convexity of the brain (Rockhill et al., 2007). The location of meningioma can predict the symptomatology, which could result in significant morbidity and mortality (Harter et al., 2017). However, due to the slow-growing nature, meningiomas are usually asymptomatic, and the diagnosis is often made incidentally on neuroimaging or at an autopsy. Signs and symptoms that are typically consistent with meningioma are seizures and focal deficits which include visual changes and mental status changes (González-Martínez and Najm, 2009; Lutwak

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Table 1
Summary of studies on meningioma and psychiatric symptoms.

Author	Study	Age*	Sex	Site	Psychiatric Symptoms	Assessment	Management	Response	Remarks
Hussin et al., 2018	Case report	45	F	Bi-frontal -olfactory groove meningioma measuring $5.5 \times 5.2 \times 4.4\,cm^3$	Depressive symptoms, changes in personality (childish behavior)	MMSE; CECT	Bi-frontal craniotomy and tumor excision	Symptoms resolved after surgical excision	CECT done when symptoms worsened, MMSE scores - 21/30 & papilledema
Takeuchi et al., 2017	Case report	33	F	Posterior cranial fossa meningioma	Obsessive symptoms: worry of infection from tainted blood and repetitive confirmation, which worsened during pregnancy	YBOCS; MRA Brain	Resection	YBOCS score reduced from 34 to 10 post-resection	MRA done upon onset of headache, dizziness 1 month post-partum
Ceylan et al., 2016	Case report	55	F	Left hemisphere medial cranial fossa meningioma of $3 \times 3 \times 2\,cm^3$	Depression, anxiety, vertigo, brief episodes of disorientation, episodes of not knowing whether she was "floating in the sky or walking on the ground"	MRI Brain	Sertraline 50 mg/day Resection and Levetiracetam 500 mg/day	Improvement in symptoms post-resection.	MRI Brain done when no improvement in vertigo & dizziness after 3 months on Sertraline
Chen et al., 2016	Case letter	74	F	$46 \times 65 \times 31\,mm^3$ tumor in central anterior frontal base	Depression, anxiety, poor sleep repeatedly asked same questions about upcoming events for 2 years (Godot Syndrome)	MMSE; Clinical Dementia Rating score; HAM-A; HAM-D; MRI-Brain	Duloxetine, Sulpride and hypnotics for 1 year followed by surgical resection of tumor upon diagnosis	Symptoms of Godot Syndrome, depression and anxiety resolved after tumor resection	Patient did not require psychotropic medications on follow up 4 years later
Leo and DuBois, 2016	Case report	59	F	Bilateral frontal lobe olfactory groove meningioma	Flat affect, avolition, decreased self-care for 3 years: diagnosed as schizophrenia 1 month prior to presentation: confusion, erratic behavior, talk about 'making potions' with blurred vision and visual disturbances e.g. perceiving 'creatures'	CT Head	Fluphenazine 50 mg depot injections intramuscular every 14 days Bilateral frontal craniotomy with tumor resection	Post-resection delirium resolved; symptoms previously ascribed to schizophrenia did not re-emerge in 1-year follow-up	CT done due to confusion No psychotropic after resection
Mahapatra et al., 2016	Case report	43	F	Multiple tumors in right fronto-parietal, temporal occipital, falx in inter-hemispheric fissure, right petrous region	H/o BPAD for 23 years presented with mixed episode with psychotic symptoms	CT Head	Quetiapine 800 mg followed by haloperidol 20 mg + lithium 900 mg. Replaced by carbamazepine 600 mg and amisulpiride 600 mg. Gamma knife sterotactic surgery	Symptoms improved post-stereotactic surgery but after 8 months depressive episode treated with fluoxetine, bupropion, carbamazepine, aripiprazole	CT Head done due to crying spells, incoherent speech, disorientation disorganized & disinhibited behavior
Pranckeviciene et al., 2016	Case report	58	M	$5.0 \times 4.2 \times 4.3\,cm^3$ at Olfactory fossa	2 year of depressive disorder	CECT; MRI; Neuropsychological tests HADS	Paroxetine 60 mg/day Agomelatine 25 mg/day day; Resection	Improvement in psychiatric symptoms with resection	CECT head done after urinary incontinence, disorientation, & memory disturbance
Saha et al., 2016	Case report	42	M	Left sphenoid wing meningioma	Symptoms resembling dementia	MRI; MMSE	Surgical resection Sodium Valproate 1gDonepezil 10mg	MMSE scores improved from 14 to 22	–
van den Berg et al., 2015	Case report	29	M	Frontal lobe	Progressive behavioral changes: apathy and self-neglect	MRI	N/A	N/A	Differential diagnosis: psychotic disorder, mood disorder or personality disorder Full article in Dutch
Dautricourt et al., 2015	Case report	54	F	Left frontal lobe	Apathy, abulia, asthenia & sleep disturbance for 6 months	CT; MRI; MMSE	Fluoxetine f/b Duloxetine f/b Venlafaxine Resection	Improved depressive symptoms post-resection. No recurrence till 2 years follow up	Imaging done due to no improvement with anti-depressants & MMSE score of 19/30
Madhusoodanan et al., 2015a	Case Report	84	F	2 calcified meningioma site N/A	Irritable, aggressive, and delusional behavior	CT	Risperidone	N/A	Surgical resection not done

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Table 1 (*continued*)

Author	Study	Age*	Sex	Site	Psychiatric Symptoms	Assessment	Management	Response	Remarks
Maia-de-Oliveira et al., 2015	Case Letter	60	F	Left frontal meningioma	Reported "It was not my fault." With 2 months of agitation, sleepless, & memory loss	EEG; CT; MRI	Citalopram; Quetiapine; Olanzapine	Good response to Olanzapine	No abnormality seen on CT. MRI Brain showed meningioma
Yakhmi et al., 2015	Case series	52	M	Bi-frontal lobe	Moderate Depressive episode	CECT Head	Escitalopram Referred to neurosurgery	N/A	CECT done upon no improvement with anti-depressant & forgetfulness
		43	M	7 cm × 6.3 cm in right frontal region	Moderate Depressive episode	CECT Head	Desvenlafaxine	N/A	CECT done due to headache and forgetfulness
Arifin et al., 2014	Case report	28	M	Left fronto-parietal & left cerebellopontine angle	Personality changes, muttering to self, suicidal tendencies	CT Head	Tumor excision	Personality changes remained, aggression improved. Suicidal tendencies stopped	Symptoms diagnosed as (diagnosed as mild depression)
Arai et al., 2014	Case report	61	M	Occiptal meningioma	Onset of visual hallucinations after removal of tumor	N/A	N/A	N/A	Diabetic retinopathy with impaired visual acuity (article in Japanese)
Li et al., 2014	Case report	58	M	Olfactory groove-5.8 cm × 6.0 cm × 4.3 cm	Major Depressive Disorder	HAM-D; MMSE; MRI Brain	Sertraline upto 200 mg; Total resection	Limited improvement with anti-depressants.	2 months post-resection patient stopped sertraline. On 6 months F/U no depressive symptoms.
Liu et al., 2014(Liu et al., 2014)	Case report	64	F	Right frontal lobe meningioma	OCD developed post resection	MRI Brain	Paroxetine	OCD resolved with Paroxetine	–
Velakoulis et al., 2014	Case report	68	F	3 cm mass frontal lobe above corpus callosum	25 years of Schizophrenia 3-months of persecutory delusions, amotivation, personality change & forgetfulness	MRI Brain	Anti-psychotics	N/A	Patient free of psychosis on medication symptoms for over 10 years until symptoms started. MRI done due to headache, impairments in attention, orientation, memory, calculation, left–right orientation, praxis etc.
Zivković et al., 2014	Case report	65	F	Left fronto-temporal convexity meningioma of 5 cm	Major depression	CT Head; EEG; HADS	Anti-depressant; Total resection	6 months post-resection HADS reduced by 50% (< 7)	Depression lasted for 2 years with anti-depressant use Imaging done due to new onset seizures
Mumoli et al., 2013	Case Report	55	M	7.5 cm × 7.4 cm right frontal area	BPAD & Alcohol Abuse with onset of symptoms 2 years prior to admission	MRI	Paroxetine; Risperidone; Sodium Valproate; Resection	No response with medications. Post-resection patient maintained well.	–
Schwartz et al., 2013	Case Report	28	F	Bi-frontal meningioma	Post-partum Depression with Psychotic symptoms with onset after 1 week of delivery	Brain Imaging	Sertraline, Risperdone; Bupropion, haloperidol, Lorazepam Resection	Symptoms worsened with psychotropics	Imaging done due to worsening symptoms
Assefa et al., 2012	Case Report	26	M	3.5 × 4.5 cm petrous apex, parasellar area, retrosellar area & cerebellar peduncles	Depression anticipatory anxiety, fearfulness	CT	N/A	N/A	Patient also had complaints of global & deep-seated headache.
Pawełczyk et al., 2012	Case Report	N/A	N/A	Right frontal lobe	Mild atypical depression	N/A	N/A	N/A	Full article in Polish
Kuruppuarachchi and Seneviratne, 2011	Case Report	40	F	Left parietal lobe	Organic delusional disorder (delusion of infidelity and delusion of persecution)	N/A	Surgical removal	N/A	–
Canuet et al., 2011		41	F	Right parasagittal parietal	Schizophrenia like psychosis	MRI Brain	Risperidone + Resection	Resolved	–

(*continued on next page*)

Table 1 (*continued*)

Author	Study	Age*	Sex	Site	Psychiatric Symptoms	Assessment	Management	Response	Remarks
	Letter to editor								
Oude Elberink et al., 2011	Case Report	47	F	Frontal lobe	Histrionic personality disorder with regression & conversion	Brain Imaging	N/A	N/A	Full article in Dutch
Ciobanu et al., 2009	Case Report	68	F	Fronto-temporal right lobe	Depression	HDRS; CGI; GAF; CT Head	Anti-depressant, anxiolytic drugs, mood stabilizers Resection	Improved	Patient was maintaining well on six months follow-up
Tsai and Huang, 2009	Case Report	51	M	4.0 × 1.8 × 0.3 cm Left temporal meningioma	Generalized anxiety, depression, auditory hallucinations	MRI Brain; CT Head	Fluoxetine; Benzodiazepines; Surgical resection	Improved	On 8 years of post-surgical follow-up patient did not show any psychiatric symptoms
Radzik et al., 2009	Case Report	50	F	Olfactory groove	Depression type symptoms	N/A	Surgical resection; Flouxetine,Valproate; BZD	N/A	Full article In Polish
Rønning et al., 2007	Case Report	50	M	Fronto-basal (olfactory meningioma)	Onset of personality changes 7 to 8 years before diagnosis.	MRI Brain	Resection	Gradual recovery	In Norwegian Emotional and psychological disturbances continued first year after surgery
Khong et al., 2007	Case Report	N/A	F	N/A	Déjà vu auditory hallucinations post-partum period	CT Head	Steroids; Anti-convulsants, craniotomy	N/A	(Full paper N/A) Meningioma mimicking puerperal psychosis
Wessling et al., 2006	Case Report	29	M	Bi-frontal	Anton syndrome	CT Head	Resection	N/A	Patient was already admitted in psychiatric care
Jähnel, 2003	Case Report	64	F	Right temporal-parietal	Depressive symptoms, later developed symptoms of acute schizophreniform psychosis	Brain Imaging	Neuroleptics and resection	Remission of symptoms post-resection without continuation of neuroleptics	Full article in German
Chaskis et al., 2001	Case Report	76	M	Forth ventricle	Agitation, restlessness exacerbated at night/ lying down	CT Head; MRI Brain	Resection	N/A	–
Hutchinson et al., 1998	Case Report	N/A	N/A	Anterior cranial fossa	Psychotic symptoms, cognitive impairment	N/A	N/A	N/A	Full article N/A
Eichhorn and Hofmann, 1998	Case Report	N/A	N/A	Frontal lobe	Depression	N/A	N/A	N/A	In German
Nagaratnam et al., 1996	Case Report	84	F	Right frontal	Musical and visual hallucination	N/A	N/A	N/A	Onset of hallucination with recurrence of meningioma
Fennig et al., 1994	Case report	43	F	Right frontal parasagittal	Capgras syndrome	N/A	Resection of tumor	N/A	In Hebrew Psychiatric symptoms resolved post resection
Nickell, 1994	Case report	39	F	Multiple	Panic attacks, complex partial seizure	MRI Brain	Carbamazepine	N/A	No response to imipramine, fluoxetine. Remission with carbamazepine
Kim, 1991	Case report	80	M	Frontal	Post-ictal capgras syndrome	N/A	N/A	N/A	–
Malek-Ahmadi and Sedler, 1989	Case report	Elderly	F	Small meningioma	Depression	N/A	ECT	N/A	No neurological symptoms of meningioma
Keshavan et al., 1988	Case report	43	M	Right frontal lobe extending to midline	Musical hallucination following tumor resection	CT Head	Resection; Carbamazepine 300 mg; Desipramine 150mg	Improved	Reduction in symptoms with medication without complete remission
		37	M	9 cm; Left frontal	Depression	CT Head	Tumor resection		

(*continued on next page*)

Table 1 (*continued*)

Author	Study	Age*	Sex	Site	Psychiatric Symptoms	Assessment	Management	Response	Remarks
Maurice-Williams and Dunwoody, 1988	Case reports							Recovered with occ. seizure episodes	4 years after depressive symptoms, focal neurological signs
		29	M	Bi-frontal	Depression	CT Head	N/A	Prior to CT head, within 7 days of admission, rapid deterioration, declared brain dead.	1 year after depressive symptoms had urine incontinence, headache
Ghadirian et al., 1986	Case report	69	F	Right temporal lobe meningioma	Anxiety attacks with depersonalization, visual perceptual disturbances	CT Head	Tumor resection	Complete recovery post-resection	–
Reiser and Swigar, 1984	Case report	Adolescent	F	Thoracic spinal cord meningioma	Anorexia nervosa	N/A	N/A	N/A	–
Maurice-Williams and Sinar, 1984	Case report	62	F	Left Frontal meningioma	Agitated depression, epilepsy obsessive thoughts	CT Head	Phenobarbitone, phenytoin prior to diagnosis of tumor. Bi-frontal leucotomy	Complete recovery post-op	–
Lahmeyer, 1982	Case report	61	F	Bilateral frontal	Apathetic depression	N/A	Amphetamines prior to diagnosis of meningioma	N/A	Irreversible neurological symptoms can be treated with amphetamines
Hunter et al., 1968	Case series	62	F	Frontal	Slow, forgetfulness, anergia	CT head; Gamma scan; EEG	Resection	Premorbid functioning on 12 months follow up	C/o anosmia, paraosmia continued
		65	F	Frontal	Seizures, apathy, aggression, somnolence, weight loss	CT head; Gamma scan; EEG	Partial resection of tumor	Improvement in spontaneity, speech post-op.	Dense amnesia present. Status epilepticus 5 months post-op
		75	F	Frontal	Bizarre bodily sensation, auditory hallucination, violent behavior	CT head; Gamma scan; EEG	Partial resection	Pt failed to recover consciousness post-operatively.	Optic atrophy noted 30 years after admission. On evaluation meningioma seen

BPAD: Bipolar Affected Disorder; CECT: Contrast Enhanced Computed Tomography; CGI: Clinical Global Impression; F: Female; F/U: Follow up; N/A: Not Available GAF: General Assessment of Functioning; HADS: Hospital Anxiety Depression Scale; HAM-D: Hamilton Scale for Depression; HDRS: Hamilton Depression Rating Scale; M:Male; MMSE: Mini Mental State Examination; MRA: Magnetic Resonance Angiography; HAM-A: Hamilton Scale for Anxiety; OCD: Obsessive Compulsive Disorder; YBOCS: Yale Brown Obsessive Compulsive Scale.

* age in years.

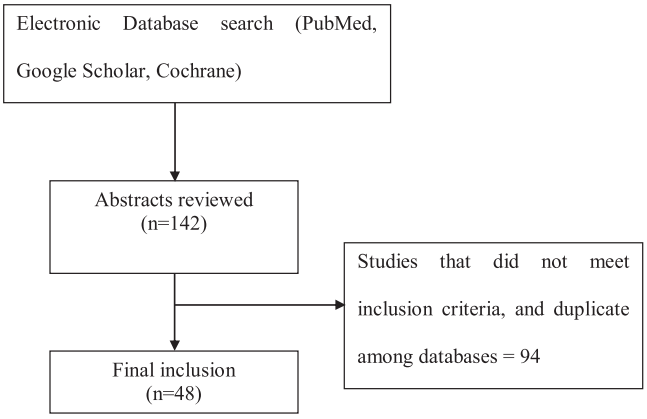

Fig. 1. Flowchart showing the number of studies.

et al., 2011; Meskal et al., 2016). The psychiatric signs and symptoms seen can range from mood symptoms, psychosis, memory issues, personality changes, anxiety to anorexia nervosa (Madhusoodanan et al., 2015a,b). The presenting signs and symptoms depend on the location of the tumor. A tumor in the dorsolateral prefrontal region typically leads to deficits in executive function and a tumor in the orbitofrontal region leads to disinhibition. Similarly, a medial-frontal region tumor may lead to apathy or abulia and temporal-limbic tumors may present with psychosis (Filley and Kleinschmidt-DeMasters, 1995). In a historical prospective study with 6,996,978 patients, within five years of index admission, 14,544 were found to have an intracranial tumor of which 7744 were a meningioma (Tringale et al., 2016). The risk for diagnosis of any intracranial tumor within five years (hazard ratio) was 1.61 (95% CI, 1.28–2.04) for bipolar disorder, 1.59 (95% CI, 1.41–1.72) for anxiety disorder, and 1.34 (95% CI, 1.25–1.43) for depression. This shows that there is an existence of association of psychiatric symptoms with brain tumors especially meningioma. However, whether these symptoms were a response to the stressors, such as coping with the diagnosis and management of the tumor or they were the presenting features of the tumor itself, cannot be commented upon with such large-scale studies. If psychiatric symptoms are the presenting features, it would have a massive implication in the early diagnosis of brain tumors. Moreover, it would help in understanding the biological basis of psychiatric symptoms, depending on whether they are simply mass effects or they indicate abnormalities in the brain networks even before the appearance of a visible mass. Recent studies have shown that there are changes in the brain topology post-irradiation in carcinoma, but these changes could be present before any therapy (Bahrami et al., 2017). Such theories have been tested in depressed individuals pre-chemotherapy, in whom whole-brain metabolic networks are seen to be affected prior to chemotherapy (Fang et al., 2016). The abnormalities in brain topology are being evaluated in other illnesses such as Huntington's disease and traumatic brain injury (Caeyenberghs et al., 2017; Fang et al., 2016; Harrington et al., 2015). The study of individual cases with a slow-growing tumor such as meningioma provides a fertile ground for conducting initial studies, which could serve as a guide to the various psychiatric manifestations associated with brain tumors. Thus, the current review has targeted the individual case reports, case letters and case series on psychiatric symptoms and meningioma.

2. Methodology

The PRISMA guidelines for systematic reviews and meta-analysis were used for the literature search following a systematic and structured approach (Moher et al., 2009). Major medical, health and psychology literature databases including PubMed, MEDLINE, PsycINFO, Cochrane database and Google Scholar were used, and the search included all publication years (till September 2018). The keywords used for the systematic search were: ("meningioma" AND "psychiatric symptoms" OR "psychosis" OR "depression" OR" mania" "bipolar disorder" OR "obsessive-compulsive disorder"). All studies (case reports, case letters, and case series) conducted in any population involving any age group which reported on the relationship between meningioma and psychiatric symptoms or disorders were considered eligible for the present review. Exclusion criteria included reviews and opinions, although their reference lists were searched for any studies not retrieved by the electronic search. To conduct a comprehensive review, studies which were in languages other than English were included if the abstract was able to provide information on the location of the tumor and associated psychiatric symptoms. Studies which reported the safety and efficacy of various interventions such as ECT in meningioma were excluded. The studies which reported cognitive impairment in patients with meningioma were also excluded.

Upon completion of the electronic database search, titles and abstracts of the identified articles they were assessed for their suitability to be included in the review. Additional searches were also conducted in other "grey" literature databases such as Google Scholar. After assessing the titles and abstracts, the full text of the articles deemed suitable if available were retrieved for further examination of the contents of the studies. Furthermore, the reference lists of the selected articles were also examined for additional suitable publications that might have been overlooked in the previous search. Data extraction was carried out under the following headings (as applicable): type of study, site of meningioma, age, sex, psychiatric symptoms, and mode of investigation, mode of treatment and extent of improvement. Table 1 contains a detailed description of all the articles included in this review.

3. Results

The initial search led to 142 studies from all the databases. Overall, 94 studies were excluded. A total of 48 studies were included after preliminary screening (Fig. 1).

All the studies included in this review were either case reports, case-letters or case series (maximum of 3 cases) as shown in Table 1. Eight of the case reports included in this review were in languages other than English and had been included in the review. Full-length articles for 3 case reports were unavailable but have been included in the review as the information on tumor location, and associated symptoms were available from the abstract. The total number of cases from all the case report and series was 52. The youngest case reported was an adolescent girl. The oldest individual was 84 years old. The mean (SD) age was 53.24 (15.66) years. Among 52 cases 31 were females, 18 were male and 3 of the case reports did not have information regarding the gender of the patients.

The commonest location of the tumor was in the frontal lobe, with about thirty cases reporting tumor located in that region. The commonest symptoms seen in frontal lobe meningioma were symptoms of depression (Eichhorn and Hofmann, 1998; Lahmeyer, 1982; Maurice-Williams and Dunwoody, 1988; Radzik et al., 2009; Schwartz et al., 2013; Yakhmi et al., 2015; Zivković et al., 2014). A case also showed associated Godot syndrome along with depressive symptoms (Chen et al., 2016). Godot syndrome is characterized by severe anxiety, which is associated with repeated questioning about upcoming events, usually seen in patients with dementia. Apathy along with other changes in personality, typically involving histrionic personality were seen in some frontal tumors (Dautricourt et al., 2015; Oude Elberink et al., 2011; van den Berg et al., 2015). Atypical depression and depression associated with agitation were seen in three of the cases (Maia-de-Oliveira et al., 2015; Maurice-Williams and Sinar, 1984; Pawełczyk et al., 2012). Another patient with 25 years of schizophrenia, was found with a frontal lobe tumor above corpus callosum when the patient was evaluated after three months of personality changes, forgetfulness and re-emergence of psychotic symptoms (Velakoulis et al., 2014). Obsessive symptoms were seen in tumor in the right as well as the left frontal lobe (Liu et al.,

2014; Maurice-Williams and Dunwoody, 1988). Right frontal lobe tumors were associated with bipolar disorder, alcohol abuse and musical and visual hallucinations (Mumoli et al., 2013; Nagaratnam et al., 1996). Interestingly, another report showed musical hallucination after resection of a right frontal lobe tumor (Keshavan et al., 1988). Capgras syndrome and Anton syndrome was also noted in frontal tumors as well (Fennig et al., 1994; Kim, 1991; Wessling et al., 2006). Six reports had tumors located in the olfactory groove. Olfactory groove tumors had been found to be associated with the onset of personality changes (Rønning et al., 2007). The olfactory groove tumors were commonly associated with depression (Hussin et al., 2018; Li et al., 2014; Pranckeviciene et al., 2016; Radzik et al., 2009). A case of the bilateral frontal lobe, olfactory groove tumor showed symptoms of flattened affect, avolition, decreased self-care for three years, which was initially diagnosed as schizophrenia (Leo and DuBois, 2016). Three cases had tumors located in the temporal lobe. One of those cases had depression (Zivković et al., 2014). Whereas, another case with a right temporal lobe tumor had anxiety with depersonalization and visual disturbances (Ghadirian et al., 1986). Another case with temporal lobe tumor also reported generalized anxiety and depression with hallucinations (Tsai and Huang, 2009). A posterior cranial fossa tumor was associated with obsessive symptoms, in which the worry of infection from tainted blood and repetitive confirmation was seen to worsen with pregnancy (Takeuchi et al., 2017). Anterior cranial fossa tumor was seen to have psychotic symptoms with cognitive impairment (Hutchinson et al., 1998). A patient with tumor located in medial cranial fossa showed symptoms of depression, anxiety, vertigo, brief episodes of disorientation, and episodes described as not knowing whether she was “floating in the sky or walking on the ground” (Ceylan et al., 2016). A tumor in the occipital lobe showed an onset of visual hallucination after resection of the tumor, although the patient also had a history of diabetic retinopathy with impaired visual acuity (Arai et al., 2014). Other regions such as the fourth ventricle tumor was associated with agitation and restlessness exacerbated at night/ lying down (Chaskis et al., 2001). A right temporoparietal region tumor associated with depressive symptoms, later developed symptoms of acute schizophreniform psychosis (Jähnel, 2003). Similarly, a right para-sagittal region of the parietal lobe was found to be associated with schizophrenia-like psychosis (Canuet et al., 2011). Other reports also showed symptoms resembling dementia in a 42 years old male with meningioma in left sphenoid wing meningioma (Saha et al., 2016). Even anorexia nervosa had been seen in thoracic spinal cord meningioma in an adolescent female (Reiser and Swigar, 1984). The detailed description of the location of the tumors and psychiatric manifestations is given in Table 1.

Most of the tumors reported in the case reports presented in the review had been diagnosed with either Computed Tomography (CT) scan of the head or a Magnetic Resonance Imaging (MRI) brain. Typically brain imaging was done when the symptoms did not fit the known presentation of psychiatric illness, if there were sudden changes in behavior and personality or the symptoms which were typical did not respond to the usual line of treatment. A CT scan or MRI was also done if symptoms such as a headache, dizziness, vertigo, or other focal neurological signs appeared. The investigations and reasons behind conducting those tests have been given in Table 1.

Management involved removal of the meningioma through total or partial resection and concomitant treatment of psychiatric and behavioral disturbances with the use of anti-depressants, anti-psychotics or anti-convulsants. Typically, with the resection of the tumors, the psychiatric manifestations resolved, occasionally not requiring a continuation of the psychotropic drugs. However, some case reports have reported post-tumor resection onset of psychiatric manifestations. Most of the case reports are unclear as to whether the psychotropic agents were continued after resection of the tumor.

4. Discussion

The studies described in this review illustrate the impact of tumor location on the occurrence of psychiatric symptoms. Some common psychiatric symptoms are often seen together with tumors in particular brain regions, example, disinhibition with orbitofrontal, apathy with medial frontal, psychotic symptoms resembling mania or schizophrenia with basal frontal tumor encroaching the third ventricle and adjacent structures etc. (Filley and Kleinschmidt-DeMasters, 1995). Diencephalic and pituitary lesions lead to vegetative symptoms which can manifest as variants of depressive disorders (Madhusoodanan et al., 2015b). In the 1980s a cross-sectional study conducted in 118 patients with schizophrenia, found that one of the patients had meningioma in the left frontal lobe (Cunningham Owens et al., 1980). The patient had auditory hallucinations, delusions, and no other focal neurological signs. This could imply that meningioma was asymptomatic or perhaps the psychotic symptoms were manifestations of the tumor. The association of psychiatric symptoms with the temporal location of tumors is further supported by a recent prospective study of 57 patients with supratentorial meningioma, in which the frequency of psychiatric symptoms in the temporal group was more than in the frontal group (Bommakanti et al., 2016). Patients with frontal meningiomas predominantly had depression. The patients with basi-frontal and sphenoid wing meningioma had mania or depressive symptoms. The supra-sellar lesions and temporal convexity lesions showed symptoms of organic delusional disorder. A case-control study of 65 patients with meningioma and 31 normal controls found highest levels of apathy in the frontal group (Peng et al., 2015). When the frontal group was further divided into various regions, it was seen that after resection, apathy reduced significantly in the medial frontal group. This evidence supports the association of spatial location of the tumor and associated psychiatric symptoms.

The association of tumor lateralization and psychiatric symptoms is further strengthened through a brief report of 50 cases, which found depression, atypical depression, and unspecified psychosis, only in patients with a right frontal lobe meningioma (Lampl et al., 1995). On the other hand, the severity of depression has been reported to be more in left frontal meningioma (Lampl et al., 1995). A cross-sectional study on 74 primary brain tumor patients, of which 11 meningiomas in the right hemisphere and 13 in left hemisphere found right hemisphere tumors had a significantly higher mean anxiety scores compared to those in the left hemisphere (A. Mainio et al., 2003). When the tumors were resected, level of anxiety declined in patients with a tumor in the right hemisphere. However, the decline in anxiety was not found in the tumor in left hemisphere even after resection and follow up. It is also seen that larger tumors are associated more with psychiatric symptoms (Bommakanti et al., 2016). These tumors exert their effects through pressure and edema and hence the symptoms donot tend to be localized to specific anatomical regions (Lampl et al., 1995)

On the contrary, other evidences have suggested that psychiatric symptoms do not have any localizing value (Madhusoodanan et al., 2015b). For instance, in the cases in the current review show depressive symptomatology in tumors located in frontal lobe as well as the temporal lobe. Similarly, obsessive symptoms have been noted in tumors across different regions of the brain (Liu et al., 2014; Maurice-Williams and Dunwoody, 1988). Thus, the occurrence of a particular symptom cannot pinpoint the location of a space occupying lesion. In a retrospective study of 79 patients with brain tumor, 72 patients had meningioma (Gupta and Kumar, 2004) and 21% had psychiatric symptoms in the absence of neurological symptoms but there was no correlation between brain laterality and the psychiatric symptoms. Although tumor laterality has been associated with psychiatric symptoms, some evidence exists against it, which require more extensive studies.

Finally, with regards to the various psychiatric presentation of meningioma, there are myriad psychiatric symptoms seen. As per our review depression and anxiety are commonly reported with

meningioma. The study relating to anxiety and depression with meningioma are often complicated as it is unclear whether they are causally related to the tumor or they are the consequence to the psychological response to the stress secondary to the diagnosis or treatment. A prospective cohort of 152 patients of which 89 had meningioma found moderate to severe depression in 28% and anxiety symptoms in 36% (Bunevicius et al., 2017). Severe depressive symptoms were associated with increased 5-year mortality risk of meningioma patients (HR = 7.083 [95%CI: 1.755–28.588], p = 0.006). Another prospective study of 98 cases in which 16.8% had a meningioma, reported depressive symptoms ranging from mild to major, anxiety and obsessive-compulsive disorder (Seddighi et al., 2015). Interestingly, three months post-resection there was a reduction in the prevalence of psychopathology. Similarly, a prospective longitudinal study conducted on 52 meningioma cases and 24 malignant astrocytoma cases found that although the anxiety and depression were comparable to the general population, anxiety level decreased after surgery (Goebel and Mehdorn, 2013). This evidence strengthens the association between the symptoms and tumors, yet the causality of these symptoms cannot be ascertained based on the available literature. Other symptoms reported with meningioma include, psychotic symptoms, changes in personality, changes in behavior, anorexia, etc. These symptoms though relatively rare, are still being reported in the form of case reports and series. Thus, it could be implied that there are several other psychiatric features of meningioma which are yet to be identified. This further illustrates the importance of individual case analysis.

Even the information regarding treatment is mostly derived from case reports or case series. Treatment involves removal of the tumor and concomitant treatment of psychiatric symptoms with pharmacotherapy or ECT. As reported previously in this review, some cases mentioned a complete resolution of psychiatric symptoms and discontinuation of psychotropic medications after tumors resection (Chen et al., 2016; Jähnel, 2003; Li et al., 2014). Although most of the studies in the review are unclear whether the psychotropic agents were continued post tumor removal. Frontal meningioma presenting with depressive illness appeared to have the best prognosis, with a resolution of symptoms post-resection (Arja Mainio et al., 2005). Personality disorders improved partially after a prolonged duration post-resection (Arifin et al., 2014; Rønning et al., 2007). Some reports have suggested that the use of psychotropic agents alone were able to control the behavioral issues without needing surgical resection (Madhusoodanan et al., 2015a,b). A study reported that among the 20 patients with psychiatric symptoms, around 15% did not improve, 40% improved partly and 45% improved post-resection completely (Bommakanti et al., 2016). These studies could serve to strengthen the causal association between the meningioma and occurrence of psychiatric symptoms.

Certain limitations of case reports and series are the major drawbacks which prevent definite inferences to be made. For instance, the cases vary not only regarding duration of tumor and size of the tumor, but also the exact site of the tumor. For example, reports would mention the lobe of the tumor without inquiry into the white matter tracts or grey matter regions. Hence, it is difficult to conclude as to why tumors which appear to be in the same region would produce different symptoms. Furthermore, the descriptions of psychiatric symptoms are not uniform in literature, neither is the use of diagnostic systems. Due to the heterogeneity of the cases included in the review, the current review is unable to address the question regarding the average latency from appearance of psychiatric symptom to the diagnosis of tumor and vice-versa. Thus, given all these factors, extrapolation of information gained from these case studies proves challenging at present. However, the application of newer technologies at the level of individual cases, and accompanying knowledge of the neuro-anatomical function of the underlying brain, could help us get an in-depth understanding of the relationship between meningioma and psychiatric symptoms from a biological perspective.

5. Conclusion

Psychiatric symptoms often can be the only presenting feature of meningioma. Physicians ought to have a high index of suspicion in patients who present with atypical clinical features of a psychiatric disorder, those who present with sudden changes in personality and those who do not respond to the usual mode of treatment. A thorough history, medical examination, and appropriate neuro-imaging are important for early diagnosis. Treatment employs target towards the tumor and the psychiatric symptoms. Evidence shows that psychiatric symptoms vary according to the localization and lateralization of tumors, although there are many exceptions. Further, understanding of the mechanisms by which tumors produce psychiatric symptoms is essential. With the technological advancements, studies of correlation of anatomic location and psychiatric symptoms may yield associations not previously found. This may lead to an improved understanding of the mechanisms of psychiatric symptoms, disorders and better categorization of symptom constructs in patients with meningioma and other brain tumors. Further studies with large sample size and stronger methodologies are warranted.

Conflict of interest

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