COPY

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE
AT WILMINGTON

UNITED STATES OF AMERICA,	:	**Crim. No. 1:13-cr-83-GAM-3**
	:	**Civil No. 1:20-cv-800-GAM**
Plaintiff-Respondent,	:	**HON. GERALD MCHUGH**
	:	**MAG.**
vs.	:	
	:	**SUPPLEMENTAL EXHIBITS**
AMY GONZALEZ,	:	**IN SUPPORT OF SECTION**
	:	**2255 MOTION**
Defendant-Movant.	:	

* * * * * * * * * *

COMES NOW DEFENDANT-MOVANT Amy Gonzalez and deposes and states as follows:

1.) I am the Defendant-Movant in the above entitled case and the instant proceedings pursuant to 28 U.S.C. § 2255.

2.) The attached documents are submitted as exhibits in support of paragraphs 57-59 of Claim Number Three of my section 2255 motion. Had trial counsel gotten a second opinion from an expert who cared enough to thoroughly review the "Published" research on psychiatric manifestations from meningiomas such as that suffered by Movant's father, the expert would have found not only these published, peer reviewed studies but also every one of the plethora of individual studies in the 2015 paper entitled, Psychiatric aspects of brain tumors: A review, found at https://pubmed.ncbi.nlm.nih.gov/26425442 which were and still are available thru the search engines of Google Scholar, PubMed, Ovid, Psych Info, MEDLINE, and MedScape. It defies logic to try to think that these studies, properly presented to the jury, would not have cast a reasonable doubt as to the "causation" of the deaths by

movant thru a break in the chain-of-events leading to the death of victims. Certainly, the absence of these available studies "undermines confidence" as to whether Movant would have been found guilty had they been properly presented. United States v. Kaufmann, 109 F.3d 186; 1997 U.S. App. LEXIS 5868 (3rd Cir. 1997).

I have personal knowledge of the originals of the exhibits and state that the copies truly and accurately represent said originals.

3.) I have read the foregoing and state that it is true and correct.

Signed under penalty of perjury under 28 U.S.C. § 1746 this ____ day of _____, 2021.

_____

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EXHIBITS A

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REVIEW

Psychiatric aspects of brain tumors: A review

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Abstract

Infrequently, psychiatric symptoms may be the only manifestation of brain tumors. They may present with mood symptoms, psychosis, memory problems, personality changes, anxiety, or anorexia. Symptoms may be misleading, complicating the clinical picture. A comprehensive review of the literature was conducted regarding reports of brain tumors and psychiatric symptoms from 1956-2014. Search engines used include PubMed, Ovid, Psych Info, MEDLINE, and MedScape. Search terms included psychiatric manifestations/symptoms, brain tumors/neoplasms. Our literature search yielded case reports, case studies, and case series. There are no double blind studies except for post-diagnosis/-surgery studies. Early diagnosis is critical for improved quality of life. Symptoms that suggest work-up with neuroimaging include: new-onset psychosis, mood/memory symptoms, occurrence of new or atypical symptoms, personality changes, and anorexia without body dysmorphic symptoms. This article reviews the existing literature regarding the diagnosis and management of this clinically complex condition.

Key words: Brain tumors; Psychiatric symptoms; Neuropsychiatric; Behavioral symptoms; Diagnosis; Management; Neuroimaging

Core tip: Psychiatric symptoms may rarely be the only presentation of a brain tumor. Any type of psychiatric symptoms can occur with brain tumors. Unfortunately, the symptoms generally do not have any localizing value. New onset psychosis, mood or memory symptoms, occurrence of new or atypical symptoms, personality changes and anorexia without body dysmorphic symptoms, suggest a work up including neuroimaging. Early diagnosis is

critical for improved quality of life for the patient.

Madhusoodanan S, Ting MB, Farah T, Ugur U. Psychiatric aspects of brain tumors: A review. *World J Psychiatr* 2015; 5(3): 273-285 Available from: URL: http://www.wjgnet.com/2220-3206/full/v5/i3/273.htm DOI: http://dx.doi.org/10.5498/wjp.v5.i3.273

INTRODUCTION

The majority of large studies discussing brain neoplasms and psychiatric symptoms date back to the 1930's[1]. Since psychiatric nomenclature and disease parameters change constantly, it is difficult to analyze this topic in a consistent manner.

Brain tumors are relatively common with an annual incidence of 9 per 100000 for primary brain tumors and 8.3 per 100000 for metastatic brain tumors. Brain tumors may be classified based on their histopathologic characteristics or anatomical location. There are two types of tumors: ones that are primary, originating from the brain tissue, and ones that metastasize to numerous locations throughout the brain. Because of this, metastatic tumors often present with more neuropsychiatric symptoms. The most common primary brain tumors are gliomas, which are divided into several types: astrocytomas, oligodendrogliomas, and ependymomas. The groups of brain tumors that are not from the glial tissue include meningiomas, schwannomas, craniopharyngiomas, germ cell tumors, pituitary adenomas, and pineal region tumors. Majority of all brain tumors are gliomas, accounting for 40%-55%. Tumors metastasizing to the brain account for 15%-25% of all brain tumors[2].

Most brain tumors present with specific neurologic signs due to mass effect. However, in rare cases they may present primarily with psychiatric symptoms. A study by Keschner *et al*[3] reported that 78% of 530 patients with brain tumors had psychiatric symptoms. However, 18% of the 530 presented only with these symptoms as the first clinical manifestation of a brain tumor. Due to the neuronal connections of the brain, a lesion in one region may manifest a multitude of symptoms depending on the function of the underlying neuronal foci. Symptoms of brain lesions depend on the functions of the networks underlying the affected areas[1]. For instance, a significant association has been found between anorexia symptoms and hypothalamic tumors, a probable association between psychotic symptoms and pituitary tumors, memory symptoms and thalamic tumors, and mood symptoms and frontal tumors[4].

Management of brain tumors consists of surgical resection of the tumor, stereotactic radiosurgery, radiotherapy, and chemotherapy. Treatment of the psychiatric symptoms caused by brain tumors depends on the presenting symptoms and includes antidepressants, antipsychotics, mood stabilizers, and anxiolytics[1].

Although there may be an association between some tumor locations and psychiatric symptoms, it is difficult to predict the symptoms based on the location or vice versa. This paper will explore the diverse manifestations, diagnosis, and management of brain tumors that present primarily with psychiatric symptoms.

LITERATURE REVIEW

A comprehensive review of the literature was conducted regarding reports of brain tumors and psychiatric symptoms from 1956-2014. Search engines used include PubMed, Ovid, Psych Info, MEDLINE, and MedScape. Search terms included psychiatric manifestations/symptoms, brain tumors/neoplasms. Our literature search yielded case reports, case studies, and case series. There are no double blind studies except for post-diagnosis/-surgery studies.

We found 172 cases with psychiatric symptoms. Psychiatric symptoms were assigned to 7 main categories: depressive symptoms, apathy, manic symptoms, psychosis, personality changes, eating disorders, and a miscellaneous category for the less frequently encountered symptoms. Each category will be discussed. Some reports may be included in more than one category due to combination of symptoms.

Depression (Table 1)

Depression may be seen in different stages (before, during or after diagnosis/treatment) of brain tumors. Depression was reported in 2.5%-15.4% of primary brain tumors[5]. According to Mainio *et al*[6], depression was found in 44% of all brain tumor patients, primary and metastatic, and was associated with functional impairment, cognitive dysfunction, reduced quality of life, and reduced survival[7]. It was also noted that depression was more commonly found in frontal lobe tumors[8-10]. More specifically left frontal lobe tumors were more frequently associated with depression and akinesia[11].

Apathy (Table 2)

Apathy must be distinguished from major depressive disorder and chronic fatigue syndrome. Patients presenting with apathy when asked about their mood, state that they are not depressed, but instead have chronic fatigue and lack of motivation[12]. This may be associated with a functional disconnection between the frontal lobe and paralimbic areas, or damage in these areas[13,14]. Levy *et al*[15] suggests that apathy is common in neurodegenerative disorders and is independent of depression. The diagnostic criteria for apathy suggested by Starkstein *et al*[16] include lack of motivation, diminished goal-directed behavior (lack of effort, or dependency on others to structure activity), diminished goal-directed cognition (lack of interest in learning new things or in new experiences, or lack of concern about one's personal problems), or diminished emotions (unchanging affect, or lack of emotional responsivity to positive or negative events).

Table 1 Brain tumors and depressive symptoms[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Zivković *et al*[42], 2014	Depression, impairment in memory, motivation, concentration, insomnia, increased appetite, headaches	Parietal lobe	Epidermoid tumor	Subsequent neurological symptoms led to CT scan and diagnosis of the brain tumor
Assefa *et al*[43], 2012	Depression, anxiety, insomnia, headache, nausea, vomiting, unilateral abducens palsy	Parasellar and retrosellar areas of the petrous apex, temporal lobe	Meningioma	Neurologic deficit with psychiatric symptoms
Ozdilek *et al*[44], 2011	Depression, anxiety, headache	Left temporal lobe	Glial tumor	Persistent headache led to neurologic consult and CT, and diagnosis
Cheema *et al*[45], 2010	Depression, anhedonia, low energy, insomnia, suicidal ideations	Left frontal and temporal lobe	Glioblastoma multiforme	Duration of psychiatric symptoms of 10 yr make the association of glioblastoma questionable and possibly unrelated
Bunevicius *et al*[46], 2008	Depression, Parkinsonian symptoms	Right fronto-temporal	Meningioma	Subsequent neurological symptoms led to CT scan and diagnosis of the brain tumor
Bunevicius *et al*[46], 2008	Depression, psychosis	Left temporal lobe	Intra-cerebral cyst	Refractory symptoms
Habermeyer *et al*[47], 2008	Depression, delirium	Right frontal lobe	Glioblastoma multiforme	Psychiatric and neurological symptoms at initial presentation
Oreskovic *et al*[48], 2007	Depression, attention deficit hyperactivity disorder	Suprasellar and pineal regions	Germ cell tumor	Good prognosis with chemotherapy and radiation
Moise *et al*[49], 2006	Depression, headache, memory loss	Right thalamus	Glioblastoma multiforme	Partial improvement of symptoms with surgical treatment and antidepressants
Madhusoodanan *et al*[50], 2004	Recent depressive symptoms, anger and agitation	Left parietal	High grade glial neoplasm with sporadic cells	Resolution of depressive symptoms after surgery, chemo- and radiation therapy
Kohler *et al*[51], 2001	Depressive symptoms refractory to antidepressants, following surgical resection of left frontal neurocytoma	Left lateral ventricle, left frontal encephalomalacia	Neurocytoma	Good response to ECT
Ghaziuddin *et al*[52], 1999	Depressed mood, mania, suicidal ideation, irritability, guilt, grandiosity, early insomnia, olfactory hallucinations	Brainstem (ponto-mesencephalic)	Astrocytoma	Improvement with ECT
Kaplan[53], 1997	Progressive depression and anxiety	Right frontal and parietal	Unknown	
Kugaya *et al*[54], 1996	Depressed mood, agitation, depersonalization, ideas of reference, suicidal ideation	Ependymal	Cyst	Partial removal of cyst led to complete resolution of symptoms
Griffith[55], 1995	Depression	Olfactory area	Esthesioneuroblastoma	
Filley *et al*[56], 1995	Severe depression, extensive weight loss	Left frontal	Squamous cell carcinoma	
Chipkevitch *et al*[57], 1993	Atypical anorexia nervosa, depression	Hypothalamus	Teratoma	
Fulton *et al*[58], 1992	Reduced communication, depression, seizures, neurologic signs	Right frontal lobe	Astrocytoma	Poor response to steroid treatment
Goodman *et al*[59], 1992	Late-onset depressive symptoms, left-sided Horner's syndrome	Several bi-frontal masses	Unknown	
Ko *et al*[60], 1989	Depressive symptoms, emotional lability, amnesia for recent events	Multiple metastatic left fronto-parietal lesions	Origin in right lung	No surgical intervention
Tanaghow *et al*[61], 1989	Depressed mood, social withdrawal, personal neglect, apathy	Anterior corpus callosum	Unknown	
Upadhyaya *et al*[62], 1988	Depression and delusions	Third ventricle	Colloid cyst	
Greenberg *et al*[63], 1988	Treatment-resistant depression with delusions	Left fronto-parietal	Meningioma	Good response of psychiatric symptoms to ECT
Goldstein *et al*[64], 1988	Depression	Right frontal	Meningioma	Good response to ECT
Summerfield[65], 1987	Depression, psychosomatic symptoms	Cerebellum	Hemangioblastoma	
Ghadirian *et al*[66], 1986	Depression and anxiety followed by visual hallucinations	Right temporal lobe	Meningioma	

Uribe[83], 1986	Depressive symptoms with rage episodes, forgetfulness, disturbance in short-term memory and abstract thinking, later-onset headaches, disorientation, gait unsteadiness, hemiparesis	Left temporo-parietal	Glioblastoma multiforme	
Dietch[83], 1984	Agoraphobia with panic attacks and major depression; later-onset right-sided weakness	Left fronto-parietal	Glioblastoma multiforme	Good response to imipramine, resolution of symptoms after surgery
Maurice-Williams *et al*[84], 1984	Depression, focal seizures	Frontal	Meningioma	Improvement of symptoms after tumor was removed
Fisher *et al*[85], 1983	Depression	Limbic system	CNS lymphoma	
Barbizet *et al*[86], 1982	Rage attacks, Bulimia, uninhibited and brutal sexual behavior, periods of depression with suicide attempts	Fronto-temporal	Astrocytoma	
Lahmeyer[87], 1982	Depression and urinary incontinence	Bilateral frontal	Meningioma	Good response to amphetamines
Littman *et al*[88], 1981	Depression, speech difficulties	Left temporal	Unknown	
Khuan *et al*[89], 1979	Depression, poor work performance	Right thalamus	Unknown	
Burkle *et al*[70], 1978	Depression, hypersomnia, anhedonia, low energy, poor concentration, memory lapses	Third ventricle with obstruction of lateral ventricles	Colloid cyst	
Carlson[71], 1977	Severe depression; prior history of seizures	Frontal	Meningioma	Complete resolution of symptoms after surgery
Carlson[71], 1977	Severe depression	Right frontal	Grade IV astrocytoma	Resolution of symptoms after surgery
Scherrer *et al*[72], 1974	Depression followed by euphoria, then seizures	Frontal	Unknown	
Blustein *et al*[73], 1972	Depression	Right temporal	Grade I astrocytoma	
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Post-op manic episode before resolution of symptoms
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Improvement after surgery

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006. ECT: Emission computed tomography; CT: Computed tomography.

Table 2 Brain tumors and apathy[69]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Aydin *et al*[78], 2013	Loss of self-generated behavior, irritability, disinhibition, impulsivity	Midline subfrontal region	Meningioma	Psychiatric and neurologic symptoms with consequent diagnosis of brain tumor
Filley *et al*[80], 1995	Apathy, social-withdrawal, poor self-care	Bifrontal	Benign meningioma	
Filley *et al*[80], 1995	Apathy, irritability, anomia, right hemiparesis	Left frontal lobe and genu of corpus callosum	Immunoblastic lymphoma	
Filley *et al*[80], 1995	Apathy, amnesia, poor affect	Thalamic and fornical columns	Gonadotropic cell pituitary adenoma	
Fulton *et al*[81], 1992	Loss of interest, poor concentration, withdrawal, lack of communication, neurologic signs	Left frontal lobe involving corpus callosum	Unknown	
Tanaghow *et al*[82], 1989	Depressed mood, social withdrawal, personal neglect, apathy	Anterior corpus callosum	Unknown	
Burkle *et al*[70], 1978	Depression, hypersomnia, anhedonia, low energy, poor concentration, memory lapses	Third ventricle with obstruction of lateral ventricles	Colloid cyst	
Avery[74], 1971	Euphoria, drowsiness, and apathy	Tuberculum sellae	Meningioma	Some residual psychiatric disturbance following resection
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Post-op manic episode before resolution of symptoms
Avery[74], 1971	Depression, apathy	Right cribriform plate	Meningioma	Improvement after surgery
Avery[74], 1971	Apathy, change in work behavior	Cribriform plate	Meningioma	Improvement after surgery

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

Manic symptoms (Table 3)

In addition to depression, patients with brain tumors can also present with other mood symptoms, such as mania. There are reports which show that while

Table 3 Brain tumors and manic symptoms[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Bhatia *et al*[74], 2013	Visual hallucinations, grandiosity, excessive talking, elated mood	Third ventricle	Neuroepithelial cyst	Psychiatric symptoms and diagnosis of brain tumor with no development of neurologic symptoms
Yetimalar *et al*[27], 2007	Personality change, psychomotor agitation, enhanced talkativeness and sex drive, decreased need for sleep	Pons	Cavernous angioma	Neurologic symptoms developed after the brain tumor was diagnosed
Ghaziuddin *et al*[31], 1999	Depressed mood, mania, suicidal ideation, irritability, guilt, grandiosity, early insomnia, olfactory hallucinations	Brainstem (ponto-mesencephalic)	Astrocytoma	Improvement with ECT
Mazure *et al*[29], 1999	Late-onset manic episode with psychotic features; no neurologic signs	Right temporal lobe	Glioblastoma multiforme	Good and rapid response of psychiatric symptoms to perphenazine
Filley *et al*[88], 1995	New-onset manic symptoms	Bitemporal	Glioblastoma multiforme	
Mark *et al*[75], 1991	Treatment-resistant bipolar disorder	Acoustic nerve	Neurinoma	Symptoms resolved completely after tumor resection
Greenberg *et al*[24], 1988	Manic symptoms	Brainstem	Metastases, origin unknown	
Jamieson *et al*[17], 1979	Mania	Right occipital, temporal and parietal lobes	Metastatic tumors-unknown primary source	
Scherrer *et al*[72], 1974	Recurrent manic episodes	Frontal	Unknown	
Avery[76], 1971	Mania, euphoria	Olfactory nerve	Meningioma	Some residual psychiatric disturbance following resection

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006. ECT: Emission computed tomography; CT: Computed tomography.

depression was associated with left frontal tumors, mania was found more commonly with right frontal tumors presenting with characteristics such as euphoria and underestimation of the significance of their illness[11]. Right hemisphere lesions have been reported to present as manic symptoms[17-19].

Psychosis (Table 4)

Another common psychiatric presentation of brain tumors is hallucinations and psychosis. Madhusoodanan *et al*[4] reported that while mood symptoms are the most common, being reported in 36% of the cases, psychotic symptoms were found in 22% of patients. In these cases of psychotic symptoms, the tumors were found in cerebral cortical, pituitary, pineal and posterior locations. Among these, pituitary gland was the most common location for psychotic symptoms. However, in another study, temporal lobe tumors were closely related to psychotic manifestations[8].

Personality changes (Table 5)

Frontal lobe lesions and ventricular cysts may present with personality changes. This may include disinhibition, hypersexuality, and aggressive behaviors.

Eating disorders (Table 6)

Weight loss and decreased appetite are associated with different types of malignancies, and in patients with brain tumors it may be among the first warning signs. This may be mistaken for symptoms of anorexia nervosa, particularly in young females, and can lead to a misdiagnosis. A review by Madhusoodanan *et al*[4] on associations between tumor locations and psychiatric symptoms concluded that while anorexic symptoms may be a result of tumors in numerous locations in the brain, hypothalamic neoplasms most commonly present as anorexia symptoms.

Miscellaneous symptoms (Table 7)

There are some cases of patients with brain tumors who present with a more ambiguous psychiatric history and progression of illness. Feng *et al*[20] described an 86-year-old female who presented with anomic aphasia. The patient reportedly had difficulty naming familiar objects and people for month. Her neurological exam was normal and she did not have any symptoms aside from the anomic aphasia. A brain computed tomography (CT) and magnetic resonance imaging (MRI) showed a large tumor in the left temporal lobe, compressing the left lateral ventricle and causing a midline shift. She underwent surgical resection of the tumor and radiotherapy. Pathology reports showed that the tumor was a glioblastoma multiforme. In this case, surgery and radiotherapy did not result in resolution of the anomic aphasia.

Among other less common and atypical psychiatric manifestations of brain tumor is a case of pathological laughter reported by Tsutsumi *et al*[21]. A 60-year-old female presented with abnormal laughter and left-hemiparesis. Her laughter was induced by non-specific stimuli and lasted for a few minutes. The MRI showed a ring-enhanced lesion in the subcortical area of the

Table 4 Brain tumors and psychotic symptoms[41]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Krayem *et al*[129], 2014	Psychosis, auditory hallucinations, self-injurious behavior	Right temporal lobe	Astrocytoma	Psychosis developed either from tumor recurrence or right temporal brain tissue loss post-surgery
Kaloshi *et al*[130], 2013	Visual and auditory hallucinations, spasmodic laughter, minimal spontaneous speech	Cerebellum	Glioneuronal	Partial improvement of symptoms with surgery
Arasappa *et al*[131], 2013	Lethargy, anhedonia, persecutory delusions, and third person auditory hallucinations	Fourth ventricle	Choroid plexus papilloma	Improvement with surgery
Canuet *et al*[124], 2011	Schizophrenia-like psychosis	Right parietal lobe	Meningioma	Psychosis developed 6 yr after initial surgery with tumor recurrence. Gradual improvement with antipsychotics
Bunevicius *et al*[132], 2008	Schizophrenia	Left temporal lobe	Anaplastic oligodendroglioma	Improvement with surgery
Bunevicius *et al*[133], 2008	Depression, psychosis	Left temporal lobe	Intra-cerebral cyst	Refractory symptoms
Bunevicius *et al*[134], 2008	Schizophrenia	Left temporal lobe	Glioblastoma multiforme	
Parisis *et al*[82], 2003	Peduncular hallucinosis (complex visual hallucinations), sleep impairment	Cerebellar metastases	Metastases	Mechanism thought to be extrinsic compression of posterior midbrain-pons by mass edema
Rueda-Lara *et al*[135], 2003	Delusions, hallucinations	Pituitary	Hormone producing adenoma	
Maiuri *et al*[136], 2002	Hallucinations	Posterior thalamus	Glioblastoma multiforme	Partial improvement of symptoms with surgical treatment and antidepressants
Miyazawa *et al*[83], 2001	Headaches and psychotic symptoms	Pineal	Pineal meningioma	Improvement with surgery
Miyazawa *et al*[83], 2001	Headaches and psychotic symptoms	Pituitary	Unknown	Improvement with steroid/hormone treatment
Craven[80], 2001	Acute psychotic episode	Pineal	Germinoma	
Vardar *et al*[137], 2000	Psychotic symptoms and cognitive deterioration	Right temporo-parietal	Arachnoid cyst	
Mordecai *et al*[86], 2000	Psychotic and obsessive-compulsive symptoms, left-sided weakness, diabetes insipidus, decline in academic functioning	Bilateral basal ganglia	Germinoma	
Werring *et al*[138], 1999	Visual hallucinations, palinopsia, posterior headache	Occipital	Tuberculoma	
Carson *et al*[139], 1997	Pediatric psychosis - hallucinations, aggression, violence	Third ventricle	Choroid plexus papilloma	Symptoms improved after surgical removal
Ball[140], 1996	Persecutory delusions, auditory and visual hallucinations, fluctuating levels of consciousness followed by grand-mal seizures	Cerebellopontine angle	Meningioma	
Filley *et al*[88], 1995	Psychotic symptoms (perceptual disturbances)	Temporal	Low-grade oligoastrocytoma	
Okada *et al*[142], 1992	Positive and negative psychotic symptoms	Left basal ganglia	Unknown	Positive symptoms resolved after surgical resection, but negative symptoms persisted
Trabert *et al*[143], 1990	Symptoms of anorexia followed by seizures and psychosis	Temporo-basal	Angioma	
Nagaratnam *et al*[144], 1990	Paranoid delusions	Left frontal lobe	Venous angioma	
Ko *et al*[145], 1989	Paranoid ideation, irritability, short-term memory difficulties	Left parieto-occipital metastatic lesion	Origin in right kidney	No surgical intervention due to advanced stage
Dyck[146], 1985	Auditory hallucinations	Sylvian fissure	Lipoma	
Binder[147], 1983	Sudden behavioral changes followed by paranoid delusions; no focal neurologic signs	Right lateral ventricle	Meningioma	Complete resolution of symptoms after surgical intervention
Binder[147], 1983	New-onset rage attacks on background of chronic schizophrenia	Bilateral occipital	Meningioma	Resolution of rage attacks after surgical removal
Dunn *et al*[97], 1983	Peduncular hallucinations	Midbrain compression	Cystic craniopharyngioma	Prompt resolution after drainage of cyst
Soulairac *et al*[96], 1979	Peduncular hallucinosis	Right temporal	Astrocytoma	
Buchanan *et al*[98], 1975	Pressured speech, hypomania, persecutory delusions	Lateral ventricle	Meningioma	
Blustein *et al*[73], 1972	Thought disorder, auditory hallucinations	Left parieto-occipital	Porencephalic cyst	

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

Table 5 Brain tumors and personality changes[4,5]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Lajeca-Narson[100], 2000	Personality changes and hypersexual behavior	Ventricular	Ventricular cyst	Improvement with surgery
Paul *et al*[101], 2000	Personality changes, memory impairment, poor concentration	Extramedullary with infiltration of the cerebral dura	Plasmacytoma	
Fahy *et al*[102], 1995	Frontal lobe symptoms in absence of neurological signs	Frontal	Meningioma	
Jones[103], 1993	Personality changes, aggressive behavior, and emotional lability	Ventricular	Ventricular cysts	Improvement with surgery
Fulton *et al*[55], 1992	Personality changes, walking difficulties, incontinence, neurologic signs	Frontal lobe	Multiple metastases	Poor response to steroid treatment
Fulton *et al*[55], 1992	Bizarre, disinhibited behavior, neurologic signs	Multiple left orbito-frontal and right thalamus	Astrocytoma	Poor response to steroid treatment
Fulton *et al*[55], 1992	Withdrawn, inappropriate behavior, neurologic signs	Bifrontal	Unknown	Poor response to steroid treatment
Lobosky[104], 1984	Personality changes and emotional lability	Ventricular	Ventricular cysts	Improvement with surgery
Barbizet *et al*[64], 1982	Rage attacks, Bulimia, uninhibited and brutal sexual behavior, periods of depression with suicide attempts	Fronto-temporal	Astrocytoma	

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

Table 6 Brain tumors and eating disorders[4,5]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Vad Winkler *et al*[105], 2009	Eating disorder	Pituitary gland	Craniopharyngioma	Improvement with surgery
Vad Winkler *et al*[105], 2009	Eating disorder	Third ventricle	Craniopharyngioma	Developed pituitary deficiency after surgery
Houy *et al*[106], 2007	Anorexia nervosa	Frontal side of the right sylvian valley	Cavernous hemangioma	Improvement with surgery
Lin *et al*[107], 2003	Anorexia nervosa	Hypothalamic region, third ventricle, pineal region, lateral ventricle, corpus callosum	Unknown	
Wolańczyk *et al*[108], 1997	Anorexia nervosa, delusions, catatonia	Right parietal lobe	Arachnoid cyst	
Chipkevitch *et al*[54], 1993	Atypical anorexia nervosa, depressive symptoms	Hypothalamus	Teratoma	
Berek *et al*[109], 1991	Anorexia nervosa	Third ventricle	Teratoma	
Trabert *et al*[110], 1990	Symptoms of anorexia followed by seizures and psychosis	Temporo-basal	Angioma	
Climo[110], 1982	Anorexia nervosa	Hypothalamus	Craniopharyngioma	
Weller *et al*[111], 1982	Anorexia nervosa	Pineal gland	Pinealoma	
Goldney[112], 1978	Anorexia nervosa	Hypothalamus	Craniopharyngioma	
Swann[113], 1977	Anorexia nervosa	Hypothalamus	Pinealoma	
White *et al*[114], 1977	Anorexia nervosa	Hypothalamus	Glioma	
Heron *et al*[115], 1976	Anorexia nervosa	Hypothalamus	Unknown	
Daly *et al*[116], 1973	Anorexia nervosa	Hypothalamus	Ectopic pinealoma	

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

right frontal lobe along with extensive perifocal brain edema. Upon total resection of the tumor, glioblastoma multiforme was diagnosed. Two weeks post-operative follow-up showed resolution of her pathological laughter and hemiparesis.

DIAGNOSIS

Brain tumors as the primary cause of psychiatric symptoms are a rare occurrence. The rarity of this condition, insidiousness of the disease process, vague symptomatology, variety of signs pointing to several causative factors all contribute to the diagnostic challenges. Diagnosis of psychiatric symptoms being secondary to brain tumors starts from having the clinical suspicion. Early diagnosis is critical with regards to further treatment and better quality of life[1].

A thorough medical history and physical examination may assist in the diagnosis. Subtle clues that could otherwise be missed include neurologic signs: apraxia, visual field deficits, and anomia. Personality changes, sleep disturbances, apathy, weight loss, anorexia, or

Table 7 Brain tumors and miscellaneous symptoms[4,10]

Ref.	Psychiatric symptoms	Tumor location	Tumor type	Remarks
Feng *et al*[120], 2013	Anomic aphasia	Left temporal lobe	Glioblastoma multiforme	No resolution of aphasia after surgical treatment
Hoffmann *et al*[117], 2012	Crying, spitting, biting self and others, mutism, withdrawal, sleepiness, anergia, bipolar affective disorder	Pituitary gland	Craniopharyngioma	No resolution of symptoms after surgery
Wong *et al*[118], 2012	Attacks of sensory overload and unusual familiarity	Left temporal lobe	Epidermoid tumor	
Rosenzweig *et al*[119], 2010	Epilepsy, paroxysmal ictal phonemes	Left superior temporal gyrus	Angiocentric glioma grade I	Resolution of symptoms after surgery
Tsutsumi *et al*[21], 2008	Abnormal laughter, left-hemiparesis	Right frontal lobe	Glioblastoma multiforme	Resolution of psychiatric symptoms after surgical treatment
Sokolski *et al*[120], 2003	Breakthrough manic symptoms with mild nausea and dizzy spells, daily derealisation episodes with olfactory auras	Right medial temporal, displacing right ventricle and right hippocampus	Grade IV invasive astrocytoma	Improvement of psychiatric symptoms with surgical resection
Burns *et al*[121], 2003	New-onset pedophilia	Right orbito-frontal	Unknown	
Daigneault *et al*[122], 1999	Aggression, precocious puberty and worsening seizures	Hypothalamic	Hamartoma	
Konovalov *et al*[123], 1998	Korsakoff's syndrome	Third ventricle	Colloid cyst	Complete resolution after surgical removal
Caplan *et al*[124], 1992	Intractable seizures followed by coprolalia, compulsive behaviors, aphasia	Left anterior temporal	Ganglionoma	Symptoms subsided after surgical resection
Ko *et al*[57], 1989	Expressive aphasia, short-term memory difficulties, no focal neurologic signs	Multiple metastatic left fronto-parietal lesions	Origin in right lung	
Ko *et al*[57], 1989	Deteriorating memory and disorientation to time and place, behavioral changes, visual agnosia, aphasia, self-neglect	Left parietal extending to temporal lobe with midline shift	Unknown-surgery refused- no autopsy report given	
Ribeiro *et al*[125], 1989	Bonnet syndrome, blindness	Posterior parasagittal	Meningioma	
Durst *et al*[126], 1988	Koro	Corpus callosum	Lipoma or dermoid tumor	
Binder[76], 1983	Behavioral changes, confusion with neurological signs developing after 24 h	Left thalamic	Glioblastoma multiforme	
de Bures *et al*[127], 1982	Aggressive behavior, cognitive impairment on background of chronic alcohol abuse and head injuries	Left temporal	Astrocytoma	

Adapted from Trends in Brain Cancer Research. New York: Nova Science Publishers Inc., 2006.

faltering concentration may be the first presentation of the illness. Further clues that suggest the presence of brain tumors may include psychiatric symptoms that do not fall into distinct diagnostic categories or atypical symptoms, symptoms that are refractory to treatment, and recurrence of previously controlled symptoms where other contributory factors (such as non-adherence to treatment, acute stressors, or medication changes) have been ruled out[1].

Neuroimaging is the primary diagnostic modality used to visualize the presence of brain tumors. CT and MRI are used for anatomical assessments. Magnetic resonance spectroscopy is used for the relative quantification of metabolites in different brain locations. Studies of neuronal activity related to local cerebral blood flow are done by functional MRI (fMRI). Positron emission tomography and single-photon emission computed tomography provide images by use of radionuclides[22]. For the purpose of this article, we will focus on the anatomical assessments that are routinely used in clinical practice. CT remains the modality of choice for trauma and acute hemorrhage. Its other advantages include: greater availability, fewer contraindications, and less expense. MRI offers higher resolution and is useful in evaluating necrosis, hemorrhage, cysts, tumors, and white-matter changes. It is generally superior to CT in visualizing brain tumors or other soft-tissue lesions. Functional studies are mostly used in the research setting and presently do not appear to have major advantages over CT and MRI for routine clinical setting. This may change with further refinements and clinical utility[22].

Madhusoodanan *et al*[1] recommended that neuroimaging be considered in the following conditions: new-onset psychosis, new-onset mood/memory symptoms, occurrence of new or atypical symptoms, new-onset personality changes, and anorexia without body dysmorphic symptoms. Conditions wherein neuroimaging may or may not be required include recurrence of previously controlled psychiatric symptoms and patients that are refractory to treatment[1].

Neuropsychological testing is useful in evaluating

cognitive and neuropsychological dysfunction, in documenting changes pre- and post-treatment, and in monitoring the effectiveness of rehabilitative efforts[2].

MANAGEMENT

Removal of the tumor may completely resolve the psychiatric or behavioral symptoms. Otherwise, decreasing the size of the tumor or halting its growth may also decrease these symptoms. Additionally, treating the acute mass effects such as increased intracranial pressure or hydrocephalus may improve cognitive functioning and decrease behavioral symptoms[2].

Neuropsychiatric and behavioral symptoms can persist or worsen after these interventions. Pharmacological and psychotherapeutic measures can be instituted to improve the functioning and quality of life[2].

Pharmacological management follows general therapeutic principles of tumor-free patients with similar symptoms. However, patients with brain tumors may have increased susceptibility for delirium, seizures, medication side effects, and drug-drug interactions.

Antidepressants may be beneficial in patients presenting primarily with depressive symptoms. Selective serotonin reuptake inhibitors (SSRIs) have a favorable side effect profile and less potential to cause delirium. Maprotiline and bupropion appear to have higher risk for seizures[23]. Methylphenidate has also been shown to be effective in patients with secondary depression. It was well tolerated and did not appear to have an increased risk for seizures. It was also found to be effective in patients with apathy syndrome aside from depression[24].

Mood stabilizers are useful in treating manic symptoms. Lithium may cause delirium and lower seizure threshold. Valproate, carbamazepine, oxcarbazepine, benzodiazepines, and gabapentin, having anticonvulsant properties, may be preferable alternatives[2]. A recent review explored possible neuroprotective effects of lithium in patients with brain cancer, especially when treated with radiation. Possible targets of lithium may include excitotoxicity, excessive apoptosis, reduced neurogenesis, and senescence of growth and regeneration. This effect has been shown in preliminary studies, but more research is required to confirm its benefits and clinical utility[25].

Antipsychotics may be used for treating psychotic syndromes with hallucinations, delusions, and disturbances in thought content and processes. First-generation antipsychotics were more widely used. Lower potency antipsychotics like chlorpromazine and thioridazine may be associated with increased risk for seizures and delirium. High-potency antipsychotics such as fluphenazine and haloperidol have lesser risk for seizure and delirium. First-generation antipsychotics like haloperidol and fluphenazine have a higher potential for extrapyramidal symptoms. This can be minimized by lowering the dosages or the addition of antiparkinsonian agents such as benztropine or trihexyphenidyl. However, addition of these agents also increases the risk for anticholinergic delirium. The second-generation antipsychotics may be preferred because of lower incidence of some of these side-effects. Effectiveness of these agents has been noted in some case reports[26,27]. However, clozapine and olanzapine are also associated with higher risk for seizures and delirium[28].

Other treatment modalities include electro-convulsive therapy (ECT). This may be given consideration in cases of refractory depression. Brain tumors without increased intracranial pressure (ICP) or edema can be treated safely with ECT[29-32] when appropriate precautions have been taken. Daily neurological evaluations are of paramount importance as deterioration may be subtle. High-risk patients are those with presence of large mass or multiple masses, increased intracranial pressure, edema, or mass effect. In these patients, ECT may be considered only if they are severely ill, or there is risk for harm to self or others, and other options have failed. Measures to reduce edema and the increase in ICP should be undertaken. Regardless of the risks of ECT, all patients undergoing this treatment should have ongoing consultation with the neurologist/neurosurgeon. Additionally, changes in the lesion should be taken into account during maintenance treatments, as low-risk patients may progress to high-risk[33].

Psychotherapy is also an important treatment modality. This helps to improve overall functional status, interpersonal and psychosocial stressors, and emotional and cognitive status. Anxiety and depressive symptoms are frequently present and may benefit from supportive and cognitive therapy, and psychoeducation. This is supported by a study which found that the presence of depressive symptoms was the most important predictor of quality of life among patients with brain tumors[34]. It is also important to improve coping strategies and identify maladaptive defenses that may interfere with somatic treatments[2].

DISCUSSION

Diagnosis and treatment of psychiatric symptoms of brain tumors are challenging. At initial presentation, patients may have a variety of symptoms or a clinical picture that do not fit into a diagnostic category. Symptoms may be vague, such as apathy syndrome or personality changes, or symptoms that are refractory to treatment. Psychiatric symptoms may be the only presenting symptoms of a brain tumor. These symptoms tend not to be localized to specific anatomical regions and tumors are not confined to specific subdivisions. Tumors also exert effects by pressure, edema, and diaschisis (affecting connections to distant areas of the brain). Thus, psychiatric symptoms generally have no localizing value. A possible exception as previously discussed, is hypothalamic tumors that present with anorexia without distorted body image. Neuroimaging, pituitary hormone levels, and ophthalmologic evaluation

are recommended based on the symptomatology to rule out the presence of a tumor[1,4].

Various studies describe the impact of tumor location and the variety of symptoms. Dorsolateral tumors lead to difficulties with organization and planning. Orbitofrontal tumors cause disinhibition, and medial frontal tumors cause apathy and abulia. Frontal tumors may exhibit personality changes in the patient. Diencephalic and pituitary lesions lead to vegetative symptoms. More specifically, diencephalic lesions manifest hypersomnic and hyperphagic variants of depressive disorders[8-10,35,36].

A thorough history and physical examination, high degree of clinical suspicion, and neuroimaging are keys to the diagnosis. A review[37] was conducted on the clinical- and cost-effectiveness of structural imaging (by use of CT or MRI) in patients with psychosis, especially that of first-episode psychosis. It concluded that structural neuroimaging adds little clinical information not suspected on history and physical examination that would influence management. Routine neuroimaging is not recommended.

Brain tumors may be primary or secondary, and are treated accordingly either by surgery, radiation, or chemotherapy. After the treatment of the tumor, psychiatric symptoms may either resolve or persist. From our clinical experience, we advocate that the treatment of psychiatric symptoms may begin before the treatment of the brain tumor, to improve the quality of life and coping skills. The psychotropics may be tapered gradually and discontinued after the tumor treatment. If psychiatric symptoms recur, psychotropics may be reinstated.

Studies of anxiety, depression, and somatic symptoms in brain tumors are complicated because it is unclear whether they are caused by the tumor or is a psychological response to the stress secondary to the diagnosis or treatment. Compounding the clinical conundrum is the lack of large controlled studies evaluating the psychiatric symptoms of brain tumors or their treatment modalities. Due to the relative rarity of this presentation and the wide array of manifestations, information regarding treatment is mostly derived from case reports or case series. Furthermore, the descriptions of psychiatric symptoms are not uniform in the literature. All these factors contribute to the difficulties in the analysis and extrapolation of available information. Treatment options include pharmacotherapy, psychotherapy, and ECT as discussed earlier.

A review that attempted to delineate the role of antidepressants in patients with brain tumors was unable to make recommendations due to lack of appropriate studies and cautions about the assumption of efficacy in this patient population[38]. With regards to safety, a study of SSRIs in patients with glioblastoma multiforme found neither any increased toxicity nor adverse effects on survival[39]. Methylphenidate has shown some evidence of efficacy in improving cognitive function and motivation. The side effects were minimal[24]. However, a more recent prospective, placebo-controlled trial of prophylactic d-threo-methylphenidate did not show any improvement in quality of life, with the main outcome measure being improvements in fatigue[40].

Continued treatment for persistent psychiatric symptoms is also complicated by the potential for delirium and seizures, possible side effects, drug-drug interactions, and status of the tumor and its treatment. Steroids may be associated with depression and psychosis. It is important that the treatment should be based on a multi-disciplinary team approach. Clinical specialists involved in the treatment should work closely and be aware of these issues with continued treatment, rehabilitation, and quality of life.

CONCLUSION

Psychiatric symptoms may be the only presenting feature of brain tumors. Thorough history and medical examination with a high index of suspicion are important for early diagnosis. Neuroimaging should be considered in patients presenting with new-onset psychosis or mood/memory symptoms, occurrence of new or atypical symptoms, personality changes, and anorexia without body dysmorphic symptoms. Treatment is geared towards the tumor, its complications, and the psychiatric symptoms. Management of persistent psychiatric symptoms is based on extrapolation of limited evidence, assessment of risk *vs* benefits, and understanding of potential complications related to the disease and concomitant therapy. Further investigation is needed to improve our understanding of the mechanisms by which tumors produce psychiatric symptoms. This may lead to improved understanding of the mechanisms of psychiatric disorders, advanced diagnostic modalities, better categorization of symptom constructs, and prospective trials for the management of the psychiatric symptoms in patients with brain tumors. With improvements in imaging techniques and diagnostic categorization of psychiatric symptoms, studies of correlation of anatomic location or neuronal functional groups and psychiatric symptoms may yield associations not previously found.

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EXHIBITS B

Benign brain tumours and psychiatric morbidity: a 5-years retrospective data analysis

Ramesh K. Gupta, Rajeev Kumar

Objective: To examine the psychiatric comorbidity in benign brain tumours.
Method: A retrospective (5 years) data analysis at our 500 bed teaching hospital. The diagnoses of benign brain tumours were based on the record of final diagnoses in the case records confirmed by either CT or MRI scans. Case records of patients with clearly documented history of psychiatric symptoms of several weeks to several months duration were identified only if such symptoms had antedated a diagnosis of the brain tumour. Using a specially designed proforma, two psychiatrists rated the symptoms together. We also collected data on age, gender and CT/MRI findings. Consensus was reached on all cases in regard to the psychiatric phenomenology. The symptoms were divided according to their presentation into purely neurological or psychiatric symptoms.
Results: A total of 79 patients were identified as having a primary diagnosis of benign brain tumour. There were 56 female patients and 23 male patients. Seventy-two of these had meningiomas. Fifteen (21%) of 72 meningioma cases, eight men and seven women, presented with psychiatric symptoms in the absence of neurological symptoms. Affective disorders were a common presentation. There was no correlation between brain laterality and the psychiatric comorbidity.
Conclusions: Psychiatric symptoms may be the only initial manifestations of meningiomas of the brain in a significant number of cases occurring in the fifth decade of life. Such patients must be investigated by brain imaging studies even if there are no neurological signs or symptoms.
Key words: affective illness, benign brain tumour, meningiomas, personality changes.

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It has long been known that intracranial tumours are associated with a high incidence of psychiatric symptoms, including depression, hallucinations, personality changes, emotional disturbances, and intellectual failure [1–3]. Parry [4] reported that 1/200 patients admitted to a psychiatry unit had a brain tumour. The largest series was reported by Keschner *et al.* [5] who found mental symptoms in 94% of cases with tumours of the temporal lobes, in 90% of cases with neoplasm of the frontal lobes, and in 47% of cases with infratentorial tumours. In a hospitalized psychiatric patient population at the University Clinic in Basle, Kocher *et al.* [6] found primary brain tumours in 1/1000 patients, a rate approximately 20 times that of the general population. These studies do not discuss the differential prevalence of psychiatric symptoms separately for benign and malignant tumours.

Despite the fact that psychiatric morbidity is relatively common in patients with certain brain tumours, it is

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infrequent for a psychiatrist to discover cerebral tumours in their patients since brain scans are not routinely ordered. In a prospective study, Hollister and Butros [7] ordered 337 CT or MRI scans to examine the frequency of undiagnosed conditions. They found that 28% of the patients had CT or MRI scans that were abnormal. Only two patients had brain tumours, which changed their management from psychiatric to neurosurgical.

Meningiomas are the most common benign brain tumours in adults and as such are encountered fairly often in neurosurgical practice [8]. The prevalence of meningiomas varies from 2.3 cases per 100 000 during life for the general population, to 5.5 per 100 000 if autopsy data are included. The incidence rates of the meningiomas were 1.5 and 3.1 per 100 000 for men and women, respectively, and the rates rose with increasing age.

In order to examine the psychiatric presentation associated with meningiomas, we undertook a retrospective hospital case record analysis of a consecutive series of all inpatient admissions to the departments of neurology and neurosurgery over a period of 5 years (January 1996 – March 2001) at the Canberra Hospital.

Method

The Canberra Hospital is a university general and speciality hospital with a bed capacity of 500, serving a population of approximately 340 000 in the region of the Australian Capital Territory and neighbouring New South Wales, Australia. This is an exclusive neurosurgical centre for the catchment area unless patients are referred to Sydney or other major centres.

The diagnoses of brain tumour were based on the record of final diagnoses in the case records confirmed by either CT or MRI scans. Case records of patients with clearly documented history of psychiatric symptoms of several weeks to several months duration were identified if such symptoms had antedated a diagnosis of brain tumour. Using a specially designed proforma, two psychiatrists rated the symptoms in a joint session. We also collected data on age, gender and CT/MRI findings. Consensus was reached on all cases in regard to the psychiatric phenomenology. The symptoms were divided according to their presentation into purely neurological, purely psychiatric and combination of both neurological and psychiatric. A patient was considered to suffer from anxiety or depression if the case notes recorded these terms in the context of a GP diagnosis or the need to treat such symptoms. Similarly personality change was defined as any observation by the family members of any abrupt change (e.g. apathy, aggressiveness or irritability) in established behaviour patterns. Admittedly DSM-IV or ICD-10 diagnosis was not possible in a retrospective study. The combination of neurological and psychiatric symptoms was considered to be a neurological presentation for the purpose of this analysis. In the event of ambiguity the symptoms were considered to have a neurological presentation and not psychiatric.

Results

A total of 79 patients were identified to have a primary diagnosis of benign brain tumours. There were 56 female patients and 23 male patients. Seventy-two of these patients had meningiomas. Three men and four women had non-meningioma tumours.

Of the 72 with meningioma, 15 patients (21%), eight men and seven women presented with psychiatric symptoms in the absence of neurological symptoms. The remaining 57 patients with meningioma, and all of the seven with non-meningioma had presented with clear neurological symptoms.

Five of the eight men and all the women who presented with psychiatric symptoms suffered with affective symptoms, taking the form of symptoms of depressive illness and/or anxiety, including one man who developed treatment-refractory depression and two patients with psychotic depression. Three men presented with personality-related changes.

The mean age for our patients with psychiatric symptoms and meningiomas was 60.5 years (SD ± 16.2). This is the same as for the whole group of meningioma patients.

An analysis was conducted in regard to the location of lesions (hemispheric as well as anatomical sites) and the results are shown in Table 1.

Discussion

A major methodological difficulty in this study as with many retrospective studies is that of ascertainment of psychiatric symptoms in patients' case notes. Thus it was not possible for us to allocate a DSM-III, DSM-IV or ICD-10 diagnosis.

Overall 21% of patients with meningiomas in our series were found to have psychiatric symptoms; 35% of the men who had meningiomas had presented with psychiatric symptoms as compared to 15% of women. Psychiatric comorbidity with meningiomas has been previously reported in sporadic case reports as well as in two recent studies. Lampl *et al.* [9] found similar rates as us of psychiatric symptoms among meningioma patients. Using DSM-III-R criteria they demonstrated psychiatric comorbidity in 16 of the 50 meningioma patients. Among these, nine had major depression, four atypical depression and three unspecified psychosis. Pringle and

Table 1. Location of lesions

Tumour location	Affective symptoms	Personality change
Left hemisphere	7	1
Right hemisphere	3	0
Anterior/posterior fossa	2	0
Midline/bilateral/bifrontal	3	2
Total	15	3

Whittle [10] reported higher levels of anxiety and depression in patients with meningiomas when measured on the Hospital Depression Anxiety Rating Scale compared to other intracranial neoplasms. These patients were assessed after a mean of 6.7 days of receiving a radiological diagnosis of intracranial neoplasm thus confounded by a psychological reaction to the diagnoses received. In our study, 80% of the patients who had meningiomas and had psychiatric symptoms had presented with affective symptoms taking the form of depressive illness or anxiety. Nonetheless the observation that affective symptoms, depression and anxiety are common to the presentation of meningiomas is in line with the reports of Lampl *et al.* [9] and Pringle and Whittle [10].

Lampl *et al.* [9] also reported the psychiatric comorbidity in their series and was limited to patients with right hemispheric frontal lobe meningiomas. In our study psychiatric symptoms occurred in seven of the 15 patients with meningiomas on the left side of the brain and only three patients with meningiomas on the right side. Five patients had tumours in the midline or with a bilateral location. Of two patients who had personality-related changes, one had a left frontal lobe meningioma and the other a left temporal lobe meningioma. Pringle and Whittle's cohort also appear to have a bilateral, right as well as left side, distribution of the meningiomas implicated in causing higher scores on the Hospital Depression Anxiety Rating Scale. In our data none of the patients with psychiatric symptoms had a meningioma of the base of the skull. Lampl *et al.* have observed that none of their patients with psychiatric comorbidity had meningioma at the base of the skull compared to 44% of the brain convexity meningiomas presenting with psychiatric comorbidity. Thus it would appear the laterality of brain tumour site and the psychiatric comorbidity has no definite positive correlation.

We found that for the general population and the period covered by this study, the number of meningioma cases recorded at our hospital give an overall incidence of 4.2 cases per 100 000 per year. This incidence is similar to the incidence reported in the Manitoba study [11]. Dumas Duport [12] observed 'meningiomas tend to produce chronic pictures of mental disorder and therefore tend to be missed'. The higher representation of women among all meningioma cases is consistent with the higher incidence of meningiomas in the female population in general. Although our patient population demonstrated a higher incidence of meningiomas in women than men, the number of such women with psychiatric symptoms was similar to the number of men with psychiatric symptoms. Whether this reflects a lesser chance for women with meningiomas to develop psychiatric morbidity compared to men, will need to be resolved by future, larger surveys.

According to Ron [13], there is no raised incidence of brain tumours among the psychiatrically ill, and therefore, the need for excessive caution and the routine expenses of clinical investigations should be spared. Weitzner [3] claims primary brain tumours are increasing in incidence with considerable psychosocial impact due to a direct effect of the tumour on mood, personality, cognition, perceptions, and indeed upon quality of life, as well as life expectancy. The difference between live population incidence of meningiomas and the autopsy incidence of meningiomas indicates many meningiomas remain undiagnosed and untreated. Our data support the conclusion that 'affective symptoms' and or 'personality change' occur in a considerable proportion of patients with meningiomas. The mean age (60.5) for the population of patients in this study with meningiomas who presented with psychiatric symptoms did not differ from that in the overall population of meningioma patients in our series. Lampl *et al.* [9] data refers to similar age finding. Holister and Boutros reach the conclusion that a first psychotic episode or personality change after the age of 45 years should be a sound indication for CT or MRI brain imaging in psychiatric practice. Of the 72 patients with meningiomas, 15 patients with psychiatric symptoms in our study were over the age of 45 and this lends support to this suggestion.

We conclude that psychiatric presentations are common with meningiomas occurring in the fourth decades of life and these patients may present to psychiatrists for treatment of their psychiatric problems. Such patients should be screened by CT scan or MRI to rule out benign tumours of the brain, particularly meningiomas.

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EXHIBITS C

Case Reports > CNS Spectr. 2008 Nov;13(11):950-8. doi: 10.1017/s1092852900014000.

Brain lesions manifesting as psychiatric disorders: eight cases

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Affiliations
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Abstract

Sometimes patients with organic brain lesions in neurologically silent brain areas might present only with psychiatric symptoms, such as depression, anxiety disorders, schizophrenia, anorexia nervosa, or cognitive dysfunction. This study presents eight cases of patients with brain lesions (four cases of meningiomas, one case of intracerebral cysts, one case of anaplastic oligodendroglioma, one case of multiform glioblastoma, and one case of occlusive hydrocephalus) who, for a significant period of time, were diagnosed and treated for psychiatric disorders (three cases of Alzheimer's disease, two cases of schizoaffective disorder, one case of schizophrenia, one case of depression, and one case of organic emotional lability disorder). When neurologic symptoms developed, they underwent neuroimaging studies and organic brain lesions were diagnosed. Further treatment required neurosurgical interventions. These cases show that brain tumors can be neurologically silent for a sufficient period of time and manifest as psychiatric disorders. Therefore, neuroimaging studies are needed when atypical changes in mental status or neurologic symptoms and signs develop.

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EXHIBITS D

Neurocase
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Case report

Case report: Anxiety and fear in a patient with meningioma compressing the left amygdala

Dawit Assefa, F. Nipa Haque & Albert H. Wong

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Abstract

The amygdalae are an important part of fear and anxiety circuits in the mammalian brain, involved in the encoding and storage of fear memories. In this case report we discuss a 26-year-old male patient with a temporal lobe meningioma that presented with unilateral abducens palsy, deep-seated headaches, and persistent psychiatric symptoms including depression and anticipatory anxiety. The patient's psychiatric symptoms and clinical diagnosis provided the impetus for the eventual diagnostic imaging and discovery of the intracranial lesion.

Keywords: Meningioma Amygdala Anxiety Fear Depression Neuroimaging

EXHIBITS E

e was thin his weight was just above the third percentile for his age, in marked contrast to the other patients in this series who were all 0.9 to 6.8 kg. (2 to 15 lb.) below the third percentile for weight. He responded more adequately to treatment than the others, gaining weight rapidly during the first 18 months of treatment on a "coeliac diet" in 1936 to 1938, to reach the fiftieth percentile for his age, and 1.3 kg. (3 lb.) overweight for his height. From the age of 5½ years he tolerated a free diet. At the time of the present survey he was symptom-free and 175 cm. (5 ft. 9 in.) in height. He regarded his bowels as constipated (bowel action alternate days) and ate freely of a normal diet. The serum folate level was 3.6 mμg./ml., Hb 14.2 g./100 ml., and blood film normal. It is therefore uncertain whether his original illness was in fact coeliac disease.

The comparative well-being of some of the present patients, in spite of flat or flat with mosaic proximal intestinal mucosa, is in keeping with the observation of Cooke *et al.* (1963), who found that a flat jejunal mucosa was fully compatible with a normal working life. The most likely explanation seems to be that the clinical state depends not on the severity of the lesion at any one point but on its extent down the small intestine (MacDonald, Brandborg, Flick, Trier, and Rubin, 1964) and on the function of the relatively normal ileum (Stewart *et al.*, 1967).

Nevertheless, six patients had symptoms. One patient had had tetany in adult life, but the effects of malabsorption were confined mainly to evidence of folic acid deficiency. When this form of malnutrition occurs in pregnancy it may be associated with an increased incidence of foetal abnormalities (Hibbard, 1964; Hibbard and Smithells, 1965).

Replacement therapy in the present patients was not always sufficient to restore health, and it seems that periodic investigation may be necessary throughout life. If haematological or biochemical evidence of malnutrition is found, treatment with a gluten-free diet appears more rational than the use of dietary supplements. Ideally it may be best, especially for women in the childbearing years, to keep strictly to a gluten-free diet.

It is a pleasure to thank Dr. Bernard Freedman for permission to study patient B. T.; Professor D. L. Mollin for the haematological findings; Professor I. D. P. Wootton's Department of Chemical Pathology for the biochemical data; Professor C. V. Harrison's Department of Morbid Anatomy for their painstaking work in the preparation of the intestinal biopsies; and Mr. W. Brackenbury for the macroscopic photograph and the photomicrograph.

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Three Cases of Frontal Meningiomas Presenting Psychiatrically

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Summary: The clinical presentation of three patients with meningiomas at different frontal sites is described. They had been ill for 3, 25, and 43 years before the tumour was demonstrated radiologically. Apathy, incontinence, dementia, and fits were seen in association with middle and superior frontal lesions, and may be mistaken for symptoms of involutional depression or presenile cerebral atrophy. In contrast, excitement and hallucinosis were seen in association with a basal frontal lesion, and may mimic psychotic syndromes like hypomania and schizophrenia, particularly if the tumour encroaches on the third ventricle and adjacent structures. Irreversible loss of myelin and axons in the frontal areas of brain surrounding the tumour may have contributed to the clinical picture of the syndrome shown by these patients.

Introduction

"In the later stages of those cases of tumour in which the mental deterioration is extreme the patient may make no complaints, and the symptoms of 'coarse' lesion may be so little marked as to pass unnoticed. It is obvious that under such circumstances the condition may be mistaken for ordinary dementia. . . . Again, in those rare cases of intracranial tumour in which maniacal symptoms are developed, unless the previous history and course of the case are known to the physician, the presence of a tumour may be unsuspected" (Byrom Bramwell, 1888).

Blackburn's pioneer monograph *Intracranial Tumors among the Insane* was published in 1903. It was based on the study of 29 cases found in 1,642 necropsies. The majority were what are now called meningiomas and the site of predilection was the frontal region. Such cases may still be missed for a number of reasons. McIntyre and McIntyre (1942) pointed to lack of "tumour consciousness." Morse (1920) blamed the fact that in mental hospitals "the point of view of the physician . . . is psychiatric rather than neurologic, and he is preoccupied with the mental symptoms." Furthermore, "use of the term 'organic dementia' as a sufficient designation discourages any refinement of diagnosis." To these reasons may be added lack of investigative facilities and a tendency to ignore physical causes as the basis of mental symptoms until they become obtrusive and the lesion becomes advanced.

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Here we report the cases of three patients in whom, for lack of physical signs early in their illness, the diagnosis was not made for 3, 25, and 43 years respectively. All three had frontal meningiomas and each presented a different, though in retrospect characteristic, clinical picture.

Case 1

This was a case of progressive dementia of presenile type without focal neurological signs—duration three years.

A married woman aged 62 was referred with a diagnosis of depression. Family and previous history were unremarkable.

History of Present Illness

She had had frontal headache for three years, at first intermittent and latterly continuous. Two years before admission a swelling appeared in the centre of her forehead which gradually enlarged. *X*-ray examination showed underlying cortical erosion and spiculation of the frontal bone, and the condition was attributed to a low-grade infection. She became depressed and sleepless, and, as the swelling was worrying her, it was explored superficially. At operation some necrotic bony cortex was scraped out. However, her symptoms persisted; she became slow, forgetful, and anergic. Finally, she took to her bed, where she remained for three months. Neurological examination at that time showed no abnormal physical signs, and she was transferred to psychiatric care with a diagnosis of retarded depression. It was thought she was suffering from an organic mental state, which, in conjunction with a history of frontal exostosis, suggested a meningioma. She was therefore admitted to the National Hospital for investigation.

Examination

On examination there were no abnormal physical signs apart from a fine tremor of the outstretched hands and tongue and generally brisk reflexes. Mentally she was tearful, somewhat confused, disorientated in time and place, and complained bitterly of headache. Psychological testing confirmed a fairly severe recent memory loss with evidence of global dementia without localizing features. She had a mild iron-deficiency anaemia (Hb 10.6 g./100 ml.) and a raised erythrocyte sedimentation rate of 26 mm. in one hour. Electroencephalography showed a marked slow-wave abnormality in the left frontal region.

Radiological Findings

Skull.—There was an area of enostosis and exostosis in the midline extending over about 3 cm., situated 2 cm. above the frontal sinuses. Small pathological vessels led up from both sides to this lesion. They were branches of each middle meningeal artery. The dorsum sellae was grossly decalcified and thinned, indicating raised intracranial pressure. The calcified pineal gland was displaced 0.5 cm. to the right of the midline and about 2.5 cm. posteriorly and about 1.5 cm. downwards. *Conclusions:* The appearances were of an almost midline frontal meningioma, extending more on the left than on the right, of massive dimensions as evidenced by the enormous (perhaps unique in degree) backward and downward displacement of the pineal gland, which was lying well in the posterior fossa. The appearances of the sella were consistent with long-standing raised intracranial pressure.

Left Carotid Arteriogram.—The common carotid artery was punctured, and good filling of both internal and external carotid arteries and their branches was obtained. Anterior branches of the middle meningeal artery were hypertrophied and tortuous, confirming the plain *x*-ray findings. They led up to the dura in the anterior frontal region above the frontal sinuses. The left anterior cerebral artery was displaced very grossly backwards and about 1 cm. to the right of the midline. The terminal portion of the internal carotid artery was depressed by the tumour. There was no tumour blush. The internal cerebral vein was displaced grossly downwards and backwards through the tentorium into the posterior fossa. *Conclusions:* The plain *x*-ray findings were confirmed. A massive tumour, more to the left than to the right, lay frontally and the appearances of the middle meningeal vessels, together with the plain *x*-ray changes, were those characteristically associated with a meningioma.

Gamma Scan (203 Hg, 600 μCi).—There was a very high uniform uptake in the anterior frontal region measuring about 8.5 cm. in diameter. In frontal view the mass lay across the midline, slightly more left than right.

Summary of Radiological Findings.—Enormous (about 8.5 cm. in diameter) frontal meningioma attached to bone above the frontal sinuses (see Fig. 1).

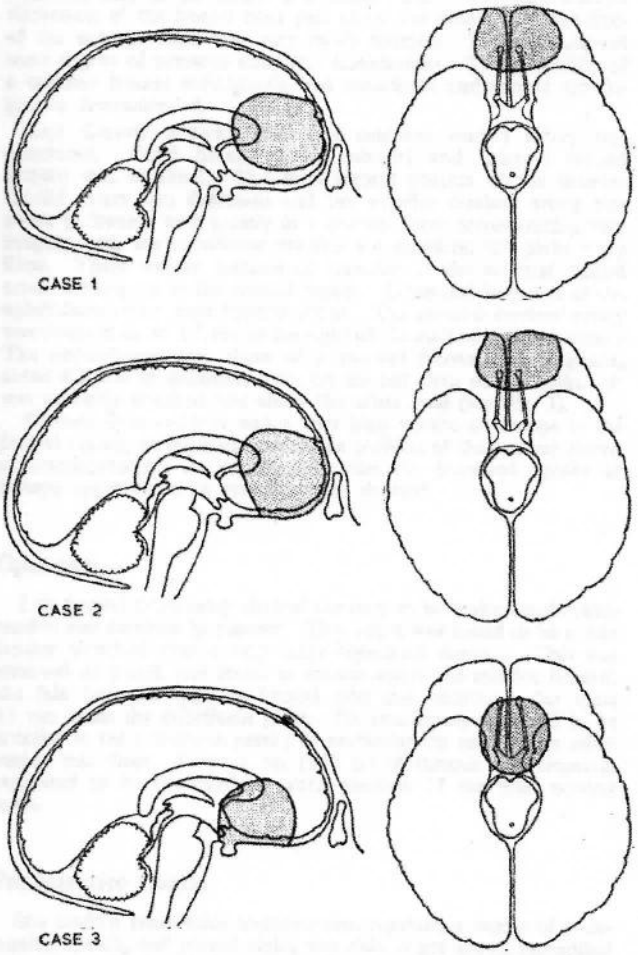

FIG. 1.—Diagrams of lateral and basal views of brain with neoplasm *in situ* as reconstructed from radiological and post-mortem appearances.

Operation

A typical parasagittal meningioma infiltrating bone was found. The tumour was extremely large (about 8 cm. in diameter), attached to the superior longitudinal sinus and the falx, and extended anteriorly to the crista galli. Some tumour appeared to be infiltrating the bone anteriorly and this was coagulated. The entire tumour and its dural attachment were removed. The frontal poles were seen to be grossly displaced backwards, but the cortex appeared undamaged.

Postoperative Course

The postoperative course was uneventful apart from a transient state of euphoria and incessant talkativeness, which subsided over the next few weeks. Two weeks after operation her verbal and performance I.Q. had risen from preoperative levels of 81 and 84 to 103 and 97, but she still showed some impairment of memory, of learning, and on certain tests of abstraction. Follow-up at 12 months showed her to be functioning at her premorbid level. However, a dense amnesia for a period of six to nine months before

operation persisted. She complained of anosmia and parosmia, presumably due to incidental damage to the olfactory nerves.

At nearly five years postoperatively there were no abnormalities in her nervous system other than total anosmia; parosmia had ceased. Her only complaint was of occasional right-sided headache. Her intellectual functions were consistently good. On formal tests her Wechsler adult intelligence scale I.Q. was 112, which was 30 points higher than before operation and a further improvement on her score soon after operation. Specific tests for a variety of frontal lobe functions, including ability to execute voluntary and skilled serial movements, and powers of abstraction, showed no remaining impairment. Her memory abilities, immediate, recent, and long-term, were above average, and learning ability for both visual and verbal material was not impaired. It was concluded that she had made a complete recovery (Brenda Clarke).

X-ray examination of skull showed recalcification of the sella, and that the pineal had moved about 2.6 cm. forwards and upwards and now lay in its normal position in both planes.

Case 2

In this case epilepsy started in adult life followed by personality change and optic atrophy—duration 25 years.

The patient was a married woman aged 65. Family and previous history were unremarkable.

History of Present Illness

At the age of 40 she started to have grand mal attacks without aura, accompanied by tongue-biting and incontinence, and followed by headache and confusion. At first they occurred weekly, by day or night, later at monthly or longer intervals. She had no recollection of attacks and knew of them only by their sequelae. At the age of 52 she had an episode of status epilepticus, and this recurred every three to four months; in between she had occasional isolated fits or a short run of serial fits. Some of the observed fits were predominantly right-sided and accompanied by a marked rise in blood pressure to 240/130 mm. Hg. Neurological investigation at this time showed her to be anosmic, obese, forgetful, and slow. Examination of cerebrospinal fluid and electroencephalography were negative. Skull *x*-ray film was interpreted as showing frontal calcification in the falx. She continued to deteriorate, became apathetic and inert, and finally incontinent and bedridden.

At 53 she was admitted to a mental hospital because she could no longer be cared for at home. There repeat *x*-ray examination of the skull was thought to show hyperostosis frontalis interna, and a diagnosis of "Morgagni's syndrome" was made. Psychological examination showed her to be fairly well preserved on verbal items but markedly impaired on performance tasks, with stereotyped errors suggestive of frontal lobe involvement. She was somnolent, aggressive when approached, and her habits were degraded. She continued to have attacks of status epilepticus and sustained two fractures in fits. During the next 12 years her weight, which initially had risen markedly, fell from 13½ to 8 stone (85.7–50.8 kg.). At this stage she was seen by one of us and transferred for investigation to the National Hospital with the provisional diagnosis of frontal meningioma.

Examination

Examination showed a severely demented, somnolent elderly woman with no spontaneous mentation. She responded to questions or commands only very slowly after much prompting and to a limited extent. She sat with her tongue protruded to the right, making purposeless repetitive movements with her right arm and leg. She appeared to be completely anosmic, and could only just distinguish between light and dark. Her pupils reacted sluggishly to light; there was bilateral optic atrophy with blurring of the disc margin on the right. Her face was asymmetrical at rest and there was a left-sided facial weakness. She was deaf, but its degree could not be assessed. There was no obvious weakness of the limbs, but she could neither stand nor walk. The reflexes were brisk and symmetrical, abdominals were absent, and plantar responses were flexor. No abnormality was found in the other systems; blood pressure was 160/100 mm. Hg.

Electroencephalogram showed a marked slow-wave disturbance maximal in the frontocentral region bilaterally with a persistent focus on the right.

Radiological Findings

Skull.—Curvilinear calcification, with convexity backwards, was present in the posterior part of the frontal region. It could be identified only in the lateral projection. There was some midline thickening of the frontal bone just above the nasion, and the floor of the anterior fossa was very much thinned. The sella showed some degree of pressure atrophy. *Conclusions:* The possibility of a calcified frontal meningioma was considered and carotid arteriography recommended.

Left Carotid Arteriogram.—The common carotid artery was punctured. Good filling of the internal and external carotid arteries was obtained. The intracerebral portion of the internal carotid artery was depressed and the anterior cerebral artery was swept backwards very grossly in a smooth curve corresponding very roughly with the curvilinear calcification noted on the plain *x*-ray films. There was an increase of branches of the external carotid artery leading up to the frontal region. Ethmoidal branches of the ophthalmic artery were hypertrophied. The anterior cerebral artery was deviated about 1.3 cm. to the right of the midline. *Conclusions:* The appearances were those of a massive bifrontal meningioma, about 6.5 cm. in diameter, more on the left than on the right. It was probably attached just above the crista galli (see Fig. 1).

Gamma Scan.—There was a very high uptake of isotope in the frontal region, corresponding with the position of the tumour shown at arteriography. In supine projection the increased uptake of isotope appeared to be symmetrically situated.

Operation

Left frontal craniotomy showed the dura to be under considerable tension and involved in tumour. The cortex was found to be a thin lamina stretched over a very large bosselated tumour. This was removed by punch and found to extend across the midline beneath the falx into the opposite frontal lobe and backwards for some 11 cm. from the cribriform plate. Its attachment appeared to be anterior to the cribriform plate; in particular the tuberculum sellae region was clear. Some 5 oz. (140 g.) of tumour was removed, estimated to be two-thirds to three-quarters of the total tumour mass.

Postoperative Course

She made a remarkable improvement, regained a degree of spontaneity, speech, and partial sight, was able to get about, recognized and conversed with relatives for the first time in a dozen years, and became partially continent. She realized she was in hospital, but had a dense amnesia for some 15 to 20 years before operation and misjudged events and ages—for example, of her children—accordingly. On an active rehabilitation programme she improved sufficiently for arrangements to be made for her to be cared for at home—after some 13 years in hospital—when after an attack of status epilepticus she succumbed some five months postoperatively.

Post-mortem Findings

Necropsy (NH 19/65. Dr. J. Peacock) showed absence of the left frontal pole. The right frontal lobe was displaced laterally by the rounded remnants of the meningioma. This mass extended from the frontal pole as far posteriorly as the coronal level of the temporal poles. It appeared to be arising principally from the inner aspect of the frontal bone, where there was an enostosis. There was no tumour in the region of the optic chiasm or hypothalamus, though the optic chiasm and nerves were very atrophic. The cerebral convolutions were somewhat flattened. The arteries at the base of the brain appeared normal. There was slight dilatation of the ventricular system with some distortion of the lateral ventricles. There was slight bilateral tentorial herniation.

Microscopical examination of the right frontal lobe, lateral and superior to the tumour, showed a relatively healthy cortex but an

abnormality of the white matter diffusely throughout the lobe. Here there was a "loose" appearance of the tissue and a marked diminution in the number of myelinated nerve fibres; the astrocytes were hypertrophied and there was a considerable astrocytic fibre formation (Fig. 2).

FIG. 2.—Coronal section of right frontal lobe of Case 2 with portion of residual tumour invaginating medial aspect. Note pale staining of white matter indicative of myelin loss (haematoxylin and van Gieson).

Microscopically the tumour was a meningioma composed of bundles and whorls of spindle-shaped cells. Mitoses were not seen. Many whorls had centres composed of collagen or of calcospherites (psammoma bodies). Some small foci of foamy cells were indicative of cellular degeneration. Fine and coarse collagenous stroma was present. Blood vessels were numerous; many had thick collagenous walls.

Case 3

In this case psychotic illness started at the age of 32, in the course of which optic atrophy followed by fits developed—duration 43 years.

The patient was a married woman aged 75. Family and previous history were unremarkable.

History of Present Illness

At the age of 32 she developed attacks which were described as follows: "She used to fall down as if she had had a stroke and then would not be able to move or speak, though she was not unconscious. Sometimes she would go into a state of coma—for instance, at meals, when she would not be able to hold her knife and fork to eat, or even hold a cup, as her arm seemed to give way. This also happened when she finished her housework. It seemed as if all the right side was affected." At the same time insidious personality change developed; she began to worry about her health and became depressed. She complained of indefinable sensations in her head, and spoke of her attacks as a feeling of losing all her strength or going into "a sleepy state." She was treated by hypnosis and imagined she was being hypnotized at a distance, wondered whether she had venereal disease, and misidentified persons about her. She began to hear voices muttering obscenities, complained to the police of being victimized, and became increasingly preoccupied with her bizarre bodily sensation and hallucinations, and attempted to rationalize them in various other delusional ways. Simultaneously it was observed that she was gaining weight.

On admission to a mental hospital some six months after the onset she was described as "hallucinated in all senses, worried by visions of wild animals and indecent sexual activities, and also by voices." She was extremely excited and voluble. At times she fell and lay "in a fixed position, saying she had been rendered incapable of moving. If one of her limbs was moved she said she had been unlocked and at once regained normal mobility." She accused the doctors and nurses of "hypnotizing her and playing with her brain" and was "somewhat annoyed in consequence." Her eyes, she complained, "were being made to work in Morse code." There were no abnormal physical signs and she was diagnosed as suffering from dementia praecox on the basis of her abnormal mental state. Later this diagnosis was changed to dementia paranoides, delusional insanity, and finally schizophrenia.

In hospital her condition remained unchanged except that her delusions, which varied, became more grandiose. She claimed she could read thoughts and so knew everything; complained of being made the subject of medical and sexual experiment, of having organs removed and others substituted, of her thoughts being transmitted by telepathy, of being played on by electricity. Her whole existence was one long torture. Two years after admission as a "certified" patient her husband's request to take her home was "barred." She was then described as sometimes quiet and pleasant, but mostly "garrulous, excitable, wildly deluded, and occasionally impulsively violent." Physical examination again showed no unequivocal abnormal signs: it was noted that her knee and ankle jerks were very brisk, and that she had attacks of "coarse fibrillary tremor of the whole body. She says she 'shivers like a dog coming out of water' and takes no notice, as she has done it for some time."

Three years after admission she complained of "being stuck all over with pins and needles; the lower part of her is frozen with cocaine, her inside is moving up and down; wonders whether she is pregnant." At night she is "subjected to the grossest interference; on one occasion they mistook her for a human telescope, but she did not know what they were looking for." Yet at times she was co-operative and worked in the ward or with a needle, at others "voluble, excitable, rambling, and absurd" but "hilarious." Some 12 years after admission she claimed to be "a lieutenant in the Army, a psychologist at Cambridge, 'the only Marconi woman,' a Chinaman's servant, Horatio Bottomley's sweetheart, half-sister to the Prince of Wales, and heiress to the British throne." She attributed her sufferings to "the 'horrorscope' having been put on her." Her habits were clean and tidy, she spent her time sewing, and there was no gross evidence of dementia supervening.

Seventeen years after admission she was still at times impulsively violent, "because she refers certain visceral hallucinations to persecution and assault by others." So accustomed were her doctors to regard all her utterances as manifestations of a sick mind that when she complained of failing sight they noted: "Still wildly deluded—she believes she cannot see her own image in the mirror." She explained it by a "syphilis germ" having got into her eyes, and described it as "like a piece of string with fibres protruding in all directions from it." After 19 years she had occasional attacks of vomiting. After 25 years she was still preoccupied with being pregnant and asked to have "the present one" removed as she already had "country houses full of children." In other respects she was also "as deluded as ever, especially about wealth, property, and her Army career," but was a good ward worker and intellectually still seemingly unimpaired.

Twenty-six years after admission ophthalmoscopy showed bilateral primary optic atrophy, the beginning symptoms of which can be traced back in her case notes some seven years; and her visual acuity was found to be less than 6/60 in each eye. The possibility of a taboparesis was considered and Wassermann and Kahn tests were performed: both were negative in blood and cerebrospinal fluid. At this time she had her first grand mal fit, and from then on she continued to have fits without aura and followed by confusion every month or more often, and on two occasions sustained fractures. The fits were apparently uninfluenced either in frequency or in severity by anticonvulsant medication. She was also observed to have narcoleptic attacks again, in which she would, for instance, fall asleep over her meals.

Thirty years after admission she was registered as blind. She had then almost doubled her weight to 14¼ stone (92 kg.). A conversation with her was recorded as follows: "She says she communicates with people in and out of hospital by telepathy and osteopathy; telepathy is inland and osteopathy overseas. Television helps her to keep dates in her mind, and 'cable vision' enables her to see people all over the world as if they were present. She was not sure whether this was lunacy, but people would be terrified if they knew what went on in her poor body and mind. 'I have all sorts of animals inside me, a tabby cat, a dragon, a platypus which lays eggs and so do I . . . there are no less than half a dozen snakes, and if anyone frightens me it makes them put out their fangs and they sting me. I am absolutely stung to death, both physically and financially—they have stung me for half a million." A later note describes her as "still gloriously deluded and full of livestock."

In view of the history of a persistent abnormal mental state, optic atrophy, and fits she was transferred to the National Hospital for further investigation with a provisional diagnosis of subfrontal meningioma.

Examination

On examination her mental state was much as described, but her delusions were less florid. She talked ceaselessly, and, being blind and deaf, uninhibitedly in a loud, raucous voice irrespective of day or night and whether there was an audience or not. She was mostly good-humoured but easily irritated. She told the examiner, "Describe me as mad." She was anosmic. There was bilateral optic atrophy, the right pupil reacted very slightly to light but not consensually, the left consensually only. She was deaf, but its degree or type could not be assessed. Her deep reflexes were brisk, abdominals absent, plantars equivocal. Gait, stance, and sensation were normal. No abnormality was found outside the nervous system other than mild hypertension. Electroencephalography was not tolerated.

Radiological Findings

Skull.—There was a gross pressure atrophy of the sella involving all the dorsum sellae and the posterior part of the floor. The appearances were of raised intracranial pressure, probably chronic, with no localizing signs. The pineal gland was faintly calcified and lay in normal position in the lateral view; it was not sufficiently calcified to be identified with certainty in the anteroposterior view.

Right Carotid Arteriogram.—The common carotid artery was punctured, and good filling of the external but poor filling of the internal carotid artery was obtained. The anterior cerebral artery was displaced somewhat backwards and upwards, and pathologically increased arterial branches of the middle meningeal artery were seen filled in the subfrontal region. Unfortunately no anteroposterior series could be taken. *Conclusion:* The appearances were of a subfrontal mass—? meningioma (see Fig. 1).

Gamma Scan (203 Hg, 600 μCi).—There was a high uptake of isotope in the subfrontal and suprasellar regions. The uptake was over a spherical zone about 6.5 cm. in diameter, mainly on the left, but just transgressing the midline. The appearances were those of a subfrontal meningioma.

Operation

The dura was not under tension. After amputation of the left frontal pole a large meningioma was seen lying on the floor of the anterior fossa. It arose extensively from the dorsum sellae and extended in all directions, entering the middle fossa area posteriorly. Some four-fifths of the tumour was removed by morcellement.

Postoperative Course.—She failed to recover consciousness, was found to have a bilateral hemiplegia, and died two days later.

Post-mortem Findings

Necropsy (NH 111/64, Dr. T. D. Meek) revealed the absence of the left frontal lobe, and showed recent infarction in the remaining distribution of both anterior cerebral arteries. When the brain was removed the tumour bed was seen to extend from the cribriform plate of the ethmoid posteriorly to the medial aspect of both sphenoidal wings. Medially the tumour extended back to the interpeduncular fossa. It completely surrounded the infundibulum, the intracranial portions of both internal carotid arteries, and the optic nerves. On the right the tumour extended out towards the right Sylvian fissure. In the right frontal lobe as far posteriorly as the corpus striatum there was a noticeable abnormality of the white matter in the regions where it was not the site of recent ischaemic necrosis (Fig. 3). This abnormality consisted of a diffuse, well-marked diminution in the number of both myelin sheaths and axons, with relative sparing of the subcortical U fibres, with astrocytic hypertrophy and the presence of abundant astrocytic fibres. The overlying cortex showed minor changes only.

Microscopically the tumour showed the appearances of a meningioma of arachnoidal type, the cells being often arranged in small whorls, supported by a coarse collagenous stroma. Mitotic figures were not found and blood vessels were not numerous.

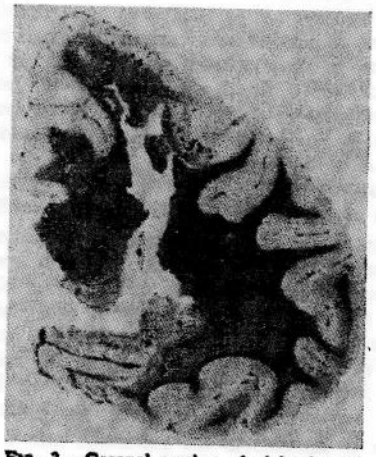

FIG. 3.—Coronal section of right frontal lobe of Case 3. Upper left: small haemorrhages in cortex and pallor of myelin indicative of recent infarction in the distribution of the anterior cerebral artery. Lower right: cortex appears normal, but deep white matter is pale when compared with that close to cortex, indicating myelin loss (Loyez stain).

Discussion

It appears that intracranial tumours are not found significantly more often in unselected necropsies performed on mental hospital patients than in those dying in general hospitals (Waggoner and Bagchi, 1953–4) despite some suggestions to the contrary (Larson, 1941; Paton and Sheppard, 1956). Klotz (1957) calculated the true incidence in both types of hospital population to be about 2–3%. However, in three respects differences are observed: (1) in the proportion of tumours diagnosed in life; (2) in the frequency with which various types of tumour occur; and (3) in the sites where tumours are most commonly found.

A survey of the literature a decade ago (Klotz, 1957) showed that about half the patients dying in mental hospitals in whom necropsy revealed an intracranial tumour were diagnosed incorrectly. Many reasons could be adduced for this, chief among them perhaps the tendency of psychiatrists to be preoccupied with what one might call "psychosyndromes" and their treatment, with lack of interest in and consequently absence of facilities for investigating the possible physical causes of patients' abnormal mental states. Furthermore, once a patient has been labelled psychiatric the case is rarely reviewed for organic possibilities, least of all in the long-stay wards of a mental hospital. To add to the psychiatrist's diagnostic difficulties not only those patients who cause social disturbance but also those in whom symptoms predominate over signs come under his care. Such a combination is found in patients who have slowly growing tumours at sites likely to cause mental changes early, such as meningiomas involving the frontal lobes (Soniat, 1951) or gliomas involving anterior midline structures (Selecki, 1964). With such lesions localizing signs may not appear until the stage of "final deterioration" as Morse (1920) called it. For these reasons frontal meningiomas are found consistently more often in mental hospital material (Zülch, 1951).

At neurological centres meningiomas account for 14–15% of all tumours (Kinnier Wilson, 1940; Russell and Rubinstein, 1959); in mental hospitals their incidence has varied from 27% (Larson, 1941) to 50% (Hoffman, 1937) to as high as

60% (Blackburn, 1903). Klotz (1957), who has collated the published series, suggests a true figure is about 33%—that is, at least twice the number seen in neurological practice. With respect to site, in neurological centres about one-fifth of tumours are found to be situated frontally (Kinnier Wilson, 1940), whereas in mental hospitals one-quarter (Patton and Sheppard, 1956) and even one-third (Morse, 1920) may be frontal.

Meningiomas occur most commonly in middle life and more often in women than in men (Cushing, 1938; Zülch, 1951). Our three patients were women. Cases 2 and 3 developed symptoms within 12 months of childbirth, an association noted by a number of authors (Bickerstaff *et al.*, 1958). They were aged 59, 40, and 32 at onset, but the diagnosis was not made until they were 62, 65, and 75, though Cases 2 and 3 had been under continuous medical observation for 12 and 42 years respectively. It is of course general experience that of all intracranial tumours meningiomas are the most likely to be missed. In the series of Wood *et al.* (1957), from the Mayo Clinic, of 300 brain tumours discovered incidentally at necropsy one-third were meningiomas. Cushing (1938) found that the interval between onset of symptoms and diagnosis was on the average eight years, and, exceptionally, as long as 20 or even 30 years. No patient remaining undiagnosed for upwards of 43 years like Case 3 has, to our knowledge, been reported before. This diagnostic time lag, astonishing even in the natural history of meningiomas, may be accounted for in her case by the early onset of "positive"—that is, psychotic—symptoms, which throughout her illness overshadowed the neurological manifestations and to the end masked the silently progressing dementia. However, it is not suggested that the tumour was actively growing throughout this time.

Presenting Symptoms

In Case 1 the diagnosis was suggested by the history of frontal exostosis, incapacitating headache, and personality change. She presented what may be called the classic form of the disease, a characteristic example of which was described as long ago as 1831 by Bright. Persistent severe headaches are rarely the presenting symptoms of a presenile atrophic process, though this was considered because of her age, dementia, and lack of localizing or lateralizing physical signs. Olivecrona (1934) placed headache first in the syndrome of frontal parasagittal meningioma, followed by insidious personality change and commonly a long history. Because the patient's sufferings were not appreciated as real, her failure to function as a housewife and her increasing apathy had been mistaken for an involutional melancholia or depression. This picture was reinforced by her persistent complaints and her tearfulness, which masked the organic syndrome of which emotional lability was one part. The fine tremor of the outstretched hands and tongue, her only physical sign, which might have been taken as further expressions of anxiety or agitation, is a recognized sign of frontal lesions (Kinnier Wilson, 1940).

Today no patient with dementia who is in long-term psychiatric care can be considered to have been adequately studied without being submitted to the range of investigations available at neurological centres. They may have to be repeated at intervals to ensure that a treatable lesion, such as a meningioma which was too small to detect at the initial examination, does not escape notice. This becomes obvious if anosmia, optic atrophy, or fits supervene, as they did in Cases 2 and 3. Case 2 was under neurological care until she was admitted to a mental hospital. In consequence it was believed that remediable conditions had been excluded.

That surgery is worth undertaking once a frontal meningioma has been demonstrated, irrespective of length of history and apparent degree of dementia, is shown by the recovery in Case 1 and the great improvement in Case 2. Case 1 had been ill for only three years but totally incapacitated for three months. Case 2 had lived a mere vegetative existence for some 15 years, being for much of that time speechless, incontinent, bed-ridden, and blind. Her inability to stand or walk without muscular weakness or reflex change—the astasia-abasia long regarded as "hysterical" but a sign of bifrontal lesions—disappeared postoperatively at the same time as she regained awareness of herself and her environment. Her vision also improved sufficiently so that she could get about again, and she became able to recognize and converse with her family. Had her home not been dispersed because it was believed she was incurable, she would have been well enough to be cared for by relatives. Cases 1 and 2 remained amnesic for the duration of their severest incapacity. Case 2 placed current events such as the ages of her children at some 15–20 years earlier in time.

In retrospect it seems possible that in Case 3 fits and other symptoms may have been aggravated if not caused by blockage of the foramina of Monro by the tumour compressing the third ventricle. However, this possibility was not considered at the time, and diagnosis was made without air study. Had it been, a ventricular shunt of the Torkildsen type, by relieving pressure in the lateral ventricles, might have sufficed at that late stage to prevent further deterioration.

Case 2 also illustrates the association of status epilepticus, either as the presenting symptom or as a recurrent phenomenon, with frontal lesions, in particular those which are bifrontal and involve the central white matter surrounding the anterior horns of the lateral ventricles (Janz, 1964). It may have been caused by direct pressure of the tumour or by the secondary changes seen in the surrounding white matter. Both Cases 2 and 3 showed evidence of extensive loss of myelinated nerve fibres from their remaining frontal lobe. In Case 2, who survived operation five months, it was not possible to be certain that this disorder had been present at the time of operation. In Case 3, however, who survived only two days, the evidence was unequivocal that extensive damage to frontal white matter had been present before operation. These changes were compatible with, but not diagnostic of, those seen in response to cerebral oedema. This is a frequent finding in white matter adjacent to neoplasms, particularly meningiomas and secondary carcinomas. Its pathophysiology is not clear, but it seems that the longer the tumour remains in situ the more likely are these irreparable changes to appear and the greater their extent. This complication adds further urgency to early diagnosis. Case 1 was fortunate not only in her comparatively short history but perhaps also that her tumour displaced the frontal lobes backwards. Her complete recovery of personality and intellectual function, confirmed by psychological testing, suggests that frontal lobe damage had either not occurred or was mild.

The postictal confusion shown by Case 2 which early in the illness led to prolonged fugue states, as well as her postictal headache, is also in keeping with a lesional epilepsy. Headache and confusion also followed fits in Case 3, but may have been due to obstructive hydrocephalus. At first they occurred singly, later in small runs. One episode of serial fits was induced by lumbar puncture performed before the diagnosis was established, when, incidentally, the cerebrospinal fluid was found to contain 260 mg. of protein per 100 ml. and an excess of globulin.

The incontinence unrelated to fits which Case 2 showed was taken for a sign of personality deterioration and loss of social sense, and was one of the reasons why she was admitted to a mental hospital. It is now known that incontinence of this kind results from medial frontal lesions which impinge on the micturition centre anterosuperiorly (Andrew and Nathan, 1964). "Morgagni's syndrome," dating from the eighteenth century and consisting of hyperostosis frontalis interna, dementia, and obesity, which was diagnosed at one stage of her illness, should now have ceased to have nosological validity (Smith and Hemphill, 1956). Like many eponymous syndromes it dies hard, though almost 150 years ago Malherbe (1833) showed that frontal meningiomas produced the clinical picture associated with it. Hyperostosis frontalis interna is in

fact bifrontal and spares the midline, while meningioma hyperostosis is nearly always unilateral or midline.

Both Cases 2 and 3 became markedly obese. Case 2 gained 4–5 stone (25.4–31.7 kg.) and Case 3 7–8 stone (44.5–50.8 kg.), which almost doubled her weight. Neither was obviously bulimic or hyperphagic. Logue *et al.* (1968) observed similar striking weight gain without corresponding increase in appetite in patients who survived rupture of an anterior cerebral artery aneurysm. Presumably in their cases the same region of the brain was damaged. The obesity of our patients, like the somnolence and anergy of Case 1, the hypertension recorded in fits in Case 2, and the narcoleptic and akinetic attacks of Case 3, was therefore probably caused by damage to hypothalamic centres at and around the anterior end of the third ventricle, whether by direct pressure or distortion. Indeed, weight gain occurring in the course of a psychiatric syndrome, especially in middle or later life, should be regarded as suspicious of underlying cerebral disease. This is in keeping with the old empirical observation that weight gain without coincident mental improvement indicates a poor prognosis (Bucknill and Tuke, 1879).

"Positive" Symptoms

In contrast with the "negative" symptoms of apathy, unconcern, and dementia which characterize lesions of the dorsal and middle portions of the frontal lobes, lesions affecting the base of the frontal lobes or orbital cortex and extending back to the infundibular region may be marked by "positive" symptoms—that is, excitement, disinhibition, and euphoria (Faust, 1966). The mental state of the patient of Arseni *et al.* (1966) was indistinguishable from hypomania, and the same was seen after orbital leucotomies (Le Beau *et al.*, 1954). It was the prevailing picture shown by Case 3 almost throughout her illness, in the course of which she developed optic atrophy after 18 years, and fits a quarter of a century later. In fact, had not Kraepelin's classification forced a division between dementia praecox or thought disorder and manic-depressive psychosis or affective disorder, "chronic mania" would have been diagnosed. Her illness began with attacks which are identifiable as narcolepsy, cataplexy, and akinesis or trance states, followed by right-sided weakness. They closely resembled those sometimes seen in patients with lesions in or around the third ventricle, such as a colloid cyst. Such patients may also have periods when they are excited and "wildly deluded," as, for instance, Kelly's (1951) Case II. In our patient the abnormal mental state persisted, though she too had times of greater excitement and rarer periods of comparative calm.

Of great theoretical interest for cerebral localization of psychiatric symptoms are her bizarre somatic illusions and hallucinations of hypochondriacal type, as well as the early, vivid, formed visual hallucinations. In contrast, auditory hallucinations remained in the background, another pointer to the "exogenous" nature of her psychosis (Bleuler *et al.*, 1966). Commensurate with her good intelligence and wit, she elaborated them richly into fantastic delusional themes. Not surprisingly, in the framework of a classification which remains predominantly symptomatic, she was diagnosed as suffering from "schizophrenia," since she showed the supposedly pathognomonic signs. Yet simultaneously she exhibited the cardinal features of "hypomania": exaltation, pressure of talk, and good humour alternating with irascibility, and Witzelsucht with a tendency to pun and "clang" associations, of which examples have been given. Doubtless some of these features, such as concreteness of thought and disinhibition, were aggravated by the secondary frontal myelin and axonal loss revealed at necropsy. However, that such states of persistent excitement with hypomanic colouring may occur independent of frontal involvement, with lesions affecting chiefly the floor of the third ventricle and adjacent structures, was shown by another patient, a woman in her sixties who presented in this way without any physical signs. Routine skull *x*-ray examination showed the typical ballooning of the pituitary fossa of chromophobe adenoma. Her "hypomania" subsided with radiotherapy, and three years later had not recurred.

Visual Hallucinations

Formed, differentiated, and complex visual hallucinations are usually taken to occur mainly in temporal lobe tumours due to irritation of the optic radiation (Huber, 1961) and then commonly accompany dreamy states with olfactory and gustatory hallucinations in the so-called uncinate fit. Lhermitte (1951), however, pointed out as early as 1922 that some patients with lesions of the upper midbrain, interpeduncular fossa, and median hypothalamic or juxtapituitary region have persistent visual hallucinations, with or without other signs of mesencephalic or diencephalic involvement. In Case 3 the tumour extended laterally to the medial aspects of the temporal lobes, but there is no record of temporal lobe type of fits. Posteriorly it reached to the interpeduncular fossa, and it is possible that irritation at this site was responsible not only for her original symptoms but also for her persistent visual hallucinosis. A like case of peduncular hallucinosis in a patient with a pituitary tumour was observed over eight years by Redlich (1912). He also developed ideas of persecution, and, like Case 3, his hallucinosis was particularly marked at night.

It should be remembered that in the early 1920s, when Case 3 fell ill, the underlying lesion could not have been confirmed even if suspected. Neither clinical knowledge nor techniques of neurological investigation were sufficiently advanced. By the time it was possible she had been for many years a "certified" patient diagnosed as schizophrenic and regarded as chronic and incurable. Furthermore, attitudes to and theories of mental illness being what they were, the relation of the subfrontal mass to her abnormal mental state might even then not have been appreciated as one of cause and effect, and operation not contemplated because of the "psychosis."

These patients were investigated under the care of Dr. C. J. Earl (Case 3, NH A20717) and Professor R. W. Gilliatt (Case 1, NH A11878, and Case 2, NH A19510) and operated on by Mr. Harvey Jackson and Mr. L. S. Walsh, whom we thank for access to case notes. The illustrations were prepared by the Department of Medical Illustration of the National Hospital.

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The Elderly in the Wrong Unit

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Summary: Patients over 65 admitted from an area of North London forming the overlapping part of the catchment areas of a geriatric unit and a psychiatric unit were studied, with particular reference to misplacement in the inappropriate hospitals service and its consequences.

The incidence of misplacement found was much lower than previously reported. In the geriatric unit 2.2% of admissions were definitely and 6.0% were probably misplaced. In the psychiatric unit 6.2% were definitely and a further 8.4% were probably misplaced. Misplacement did not materially affect the outcome. The striking differences that were found between the patterns of death and discharge in the geriatric and psychiatric units were determined principally by the type of illness leading to admission.

The frequent coexistence of mental and physical disorders in the elderly patient, which this study confirms, indicates the need for further development of effective liaison at a local level between the geriatric, psychiatric, and social services.

Introduction

Recent thinking on geriatric services has favoured the establishment of assessment units with subsequent disposal of patients according to their needs. Much of this thought has been influenced by the findings of Kidd (1962a) in his study of old people in Belfast. He found that a large number of geriatric patients suffered both mental and physical illness, that many were admitted to the inappropriate hospital, and suggested that the prognoses of these patients were worse as a result (Kidd, 1962b).

The present paper describes part of a study designed to explore the need for such an assessment unit. It was carried out in the densely populated working-class boroughs of Tottenham and Edmonton (total population 204,205, with 25,376 aged 65 years and over at the 1961 Census) in North London. This is the only overlapping part of two much more extensive and independently run geriatric and psychiatric services; it is divided between two different local authorities. The geriatric service, to be referred to subsequently as the geriatric unit, has 181 admission beds (at the North Middlesex Hospital, Edmonton, and at St. Ann's General Hospital, Tottenham), with another 79 beds in long-stay annexes. The psychiatric service, which will be called the psychiatric unit, has 77 geriatric admission beds at Claybury Hospital, Essex, with a small number of additional beds in general psychiatric admission wards at the North Middlesex Hospital and at Claybury Hospital. There are also a large number of long-stay beds at Claybury Hospital.

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Methods

Patients aged 65 and over from Tottenham or Edmonton who were admitted to the geriatric or psychiatric unit in the year from 8 May 1965 to 7 May 1966 were the subjects of the study. All admissions to the psychiatric unit were included, but a one-in-four random sample of admissions to the geriatric unit was taken so as to have roughly equal numbers. Within the first few days of admission the patients received a full psychiatric and medical examination, based on a standard form designed after a pilot study. Their behaviour was assessed separately by one of us (G. J. E.) and by the nursing staff, and recorded on the Crichton Royal Behaviour Rating Scale (Robinson, 1959). The Inglis Paired Associate Test (Inglis, 1959) was used in some cases. When necessary, patients' relatives were interviewed and their homes visited.

The course of each patient's illness was followed, and on discharge from hospital their behaviour was again assessed on the same behaviour rating scale. Six months after admission the outcome of each patient was recorded, and those who were alive were interviewed and their condition was assessed on a standard form. The results were transferred to punched cards for analysis.

The patients were classified in four different groups according to Kidd's terminology: (1) mental, (2) mental–physical, (3) physical–mental, and (4) physical. Patients in group 1 were diagnosed as suffering from psychiatric disorders only, and patients in group 4 from somatic disorders only. Patients in groups 2 and 3 were suffering from both psychiatric and somatic disorders, the first-mentioned being the main condition leading to hospital admission. Therefore in the geriatric unit groups 1 and 2 were misplaced; and in the psychiatric unit groups 3 and 4 were misplaced. One of us (G. J. E.) examined and assigned individual patients to one of the four groups, but difficult or borderline cases were placed after discussion

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE
AT WILMINGTON

UNITED STATES OF AMERICA,	:	**Crim. No. 1:13-cr-83-GAM-3**
	:	**Civil No. 1:20-cv-800-GAM**
Plaintiff-Respondent,	:	**HON. GERALD MCHUGH**
	:	**MAG.**
vs.	:	
	:	**CERTIFICATE OF FILING**
AMY GONZALEZ,	:	**AND SERVICE**
	:	
Defendant-Movant.	:	

* * * * * * * * * *

Pursuant to the principles of Houston v. Lack, 487 U.S. 266, 276 (1988), Ms Gonzalez has this day filed with the Court and served counsel for the opposing party with the required original and copies of the enclosed documents by depositing same in the prison legal mail collection box, in sealed envelopes, first class postage affixed and addressed to: **Clerk, U.S. District Court, 844 North King St Unit 18, Wilmington, DE 19801-3570** and to **United States Attorney, 1313 N Market St - PO Box 2046, Wilmington, DE 19801.**

Signed under penalty of perjury under 28 U.S.C. § 1746 this _____ day of _____, 2021.

_____

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