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REVIEW ARTICLE

Psychiatric aspects of tumours of the central nervous system

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Abstract: The incidence of brain tumours has increased in recent years. They represent the second most common cause of death attributable to neurological conditions. Although expansive brain lesions often lead to observation by Neurology or Neurosurgery, it is not uncommon for psychiatric symptoms to be the reason for initial contact with medical care. Brain tumours may present as symptomatology similar to the so-called primary, or functional, psychiatric disorders. However, in contrast to psychiatric disease in other types of cancer, where adjustment disorders predominate, organic syndromes are the most frequent diagnosis in patients with CNS tumours.
Anatomic location represents one of several factors that contribute to the nature and severity of psychiatric conditions. Tumours of the frontal lobe are more frequently associated with changes in executive function, amotivational syndrome and personality changes. Temporal tumours can trigger psychotic symptoms such as hallucinations and delusions.
The treatment of the symptomatology will essentially involve removal of the lesion whenever possible. Nevertheless, symptomatic treatment of psychiatric manifestations should always take place. Psychopharmacology, psychotherapy and psychoeducation of caregivers are the best modes of treatment.

Keywords: Central Nervous System Neoplasms; Psycho-oncology; Psychiatric Symptoms

Introduction

Psycho-oncology spans the two principal psychiatric and psychological dimensions of cancer: on the one hand, the experiences of patients and their family members over the course of the disease, and also the stress felt by care-giving professionals; on the other, the psychological, behavioural and social factors that influence risk, detection and survival of oncological disease [1].
The incidence of brain tumours has increased in recent years. They represent the second most common cause of death attributable to neurological causes, the first being stroke [2].
Brain tumours can be classified according to their nature (primary or metastatic), histology or location. Gliomas (40-55%) and meningiomas (10-20%) represent the majority of expansive intracerebral lesions. Metastatic lesions (15-25%) originate most commonly from lung and breast tumours. 30% of tumours are located in the posterior fossa, the most common supratentorial lesions being those of the frontal (22%) and temporal lobes (22%); 12% are located in the parietal lobes, 10% in the *sella turcica*, and 4% in the occipital cortex [2].
Cerebral metastases generally manifest as hemiparesis and cognitive dysfunction; unilateral hypoesthesia, ataxia and aphasia are less common symptoms [3]. The usual symptomatology of primary brain tumours – solid tumours or lymphomas – is cognitive dysfunction, headaches, vomiting, seizures and focal deficits [4]. Disease progression and the toxic effects of treatment (e.g. radiotherapy) tend to cause cognitive deterioration to worsen and, at advanced stages, demential syndromes or changes in consciousness.
While expansive brain lesions often lead to observation by Neurology or Neurosurgery, it is not uncommon for initial contact with medical care to be prompted by psychiatric symptoms. A study of 530 patients with brain tumours reported that in 18% of cases clinical presentation was psy-

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chiatric [5]. A recent analysis of patients with meningiomas indicated that 21% of the study sample had initially presented with psychiatric symptoms in the absence of neurological signs [6].

Clinical Aspects

Brain tumours may present in the form of symptoms similar to primary, or functional, psychiatric disorders. However, in contrast with what happens with regard to psychiatric illness in other types of cancer, where adjustment disorders predominate, organic syndromes are the most common diagnosis in patients with tumours of the CNS.

Although some symptoms or syndromes may be associated with dysfunction of certain parts of the brain (e.g. depression and personality changes in frontal tumours and psychosis in temporal lesions), anatomic location represents one of several factors that contribute to the nature and severity of the psychiatric picture. Fast-growing tumours are more frequently associated with agitation and psychosis, and more obvious cognitive dysfunction. Less aggressive lesions are associated with apathy, depression and incomplete personality changes. Multiple tumour sites tend to cause more significant behavioural changes. Increased intracranial pressure, a non-specific consequence of tumours of the CNS, is associated with apathy, depression, irritability, agitation and changes of consciousness.

Silent onset and few symptoms are a feature of the evolution of tumours of certain regions of the brain; lesions of the anterior part of the frontal lobes, the corpus callosum, the non-dominant parietal and temporal cortex and the posterior fossa are examples of this [2].

Frontal Lesions

The frontal lobe constitutes the most recently evolved region of the brain in phylogenetic terms and the largest in the central nervous system, representing 1/3 of its total volume. From the anatomo-functional point of view, the frontal lobe is divided into at least five specialised regions: (1) motor cortex, (2) pre-motor cortex, (3) frontal operculum, (4) para-olfactory or subcallosal zone and (5) pre-frontal cortex. The pre-frontal cortex is the region of the frontal lobe most commonly related to metacognitive abilities, executive functions and social behaviour in general. It can be divided into three distinct zones, which correspond to the dorsolateral, orbitofrontal and frontomedial cortex. In general terms, we can organise the nature of the deficits resulting from lesions in accordance with the proposed division of the pre-frontal cortex by establishing the existence of three syndromes – see Table 1. [7]

Dorsolateral, or disorganised, syndrome, characterised by impairment of executive functions, is due in the majority of cases to tumour lesions, ischaemic lesions, trauma or neurodegenerative disease of the frontal lobe [8]. **Ventromedial** syndrome, which manifests above all as apathy, is usually related to tumour lesions of midline structures (thalamus, third ventricle, hypothalamus and pituitary), and also occurs following bilateral occlusion of the anterior cerebral arteries and bilateral thalamic infarcts. Lastly, **orbitofrontal** syndrome, in which changes in behaviour and pragmatics are to the fore, is associated with tumours (e.g. inferior frontal meningiomas), as well as post-traumatic lesions, vascular lesions of the anterior cerebral artery, multiple sclerosis and fronto-temporal dementia [8].

Table 1. Frontal syndromes

DORSOLATERAL syndrome
Predominant involvement of executive functions.
Poor planning
Reduced mental flexibility
Abstraction deficit
Persistence
Apathy
Distractibility
Personal neglect
Behaviours directed at stimuli

VENTROMEDIAL syndrome
Deficit of initiative and motivation.
Apathy
Abulia
Incontinence
Gait changes

ORBITOFRONTAL syndrome
Predominance of personality changes.
Deterioration of social pragmatics
Disinhibition
Impulsiveness
Moria (foolish euphoria)
Emotional lability
Distractibility
Olfactory changes

This anatomo-functional division is rarely clear in clinical practice: pure presentations of these syndromes are uncommon. In addition, personality changes, particularly associated with frontal lesions (more than 70% of cases), may occur in disorders of diencephalic and temporal structures.

Psychotic symptoms may be present in 10% of frontal tumours. Delusions are usually fragmented and hallucinations are rarely auditory and complex, in contrast to what is most characteristic of schizophrenic psychosis [2].

Temporal lesions

In addition to frequent symptoms of the ictal sphere, tumours of the temporal region have in the past been associated with psychotic symptoms of a schizophreniform type. However, more recent reports have described atypical symptoms, not always associated with schizophrenia: vis-

ual, olfactory or tactile hallucinations, and mood swings with suicidal behaviours, with conserved affect and social interaction.

Behavioural symptoms are common in temporal lesions: personality changes have been described in more than 50% of patients. As described in lesions of the frontal lobe, psychiatric symptoms like apathy, irritability and emotional lability occur. Anxiety is also present in more than 30% of cases [2].

Parietal and occipital lesions

Lesions of the parietal or occipital cortex have been associated with psychiatric symptoms to a lesser degree.

Parietal lesions are usually associated with perceptual and motor impairments, such as astereognosis and agraphesthesia, apraxia, anosognosia, acalculia and dysgraphia [9].

25% of patients with occipital tumours present visual hallucinations – generally simple, e.g. luminous flashes. Other symptoms that have been reported – agitation, irritability, drowsiness – probably reflect non-specific manifestations of intracranial hypertension. In addition to typical findings like homonymous hemianopia, visual agnosia and prosopagnosia are also common [2].

Lesions of other structures

Diencephalic tumours often compromise structures contiguous with the limbic system; it is also common for cortico-subcortical circuits to be affected, with subsequent psychiatric manifestations. Schizophreniform [10], affective [11] and obsessive-compulsive type symptoms [12] and personality changes [13] have been reported. Behavioural changes are usual in lesions of the corpus callosum (especially genu and splenium), with an estimated prevalence of 90%. Affective symptoms predominate; personality changes and psychotic symptoms are also common [2]. Tumour lesions of the hypothalamus have been associated with changes of eating behaviour, in particular hyperphagia; clinical observations compatible with a diagnosis of anorexia nervosa have also been reported in the literature [14]. Subcortical tumours may present with a predominance of memory deficits, possibly within the framework of a subcortical-type demential syndrome [2].

Delirium

The clinical appearance of delirium includes: prodromal manifestations (restlessness, anxiety, insomnia and irritability); fluctuating evolution; distractibility; changes in state of wakefulness; disruption of sleep-wake rhythm; affective symptoms (emotional lability, sadness, distress, euphoria); sensoriperceptual changes (illusions, visual and auditory hallucinations); paranoid delusions; disorganised speech; temporo-spatial and autopsychic disorientation; memory impairments (especially of short-term memory). Onset of symptoms is acute or subacute, and the latter are transient and reversible. These chronological characteristics help differentiate it from demential syndrome. In their early stages, cases of hypoactive delirium may be interpreted as depression. In rare situations, delirium may be the initial manifestation of neoplastic lesions in the CNS [15].

The approach to delirium includes from the start identifying and correcting, wherever possible, underlying causes (see Table 2).

Table 2. Causes of delirium in the oncological patient

Direct brain injury	Primary brain tumour, cerebral metastasis
Metabolic encephalopathy due to organ failure	Liver, kidney, lung, thyroid, adrenal
Electrolyte disturbances	Sodium, potassium, calcium, glucose
Toxic effects of treatment	Narcotic analgesics, anticholinergics, antihistamines, corticosteroids, phenothiazines, chemotherapy agents, radiotherapy
Infection	Septicaemia
Haematological disturbances	Anaemia (microcytic, macrocytic), coagulopathy
Nutrition	Malnutrition, ↓thiamine, ↓folic acid or ↓vitamin B12
Other	Pain, constipation, paraneoplastic syndromes

(Adapted from Breitbart and Cohen, 1998)

Support measures may be sufficient, in particular environmental optimisation: quiet rooms with soft lighting, with personal objects and chronological references (clock, calendar). The presence of family members may prove particularly calming. In the case of prior sensory dysfunction requiring visual or auditory prostheses, especially in the elderly, these should be available at all times. Physical restraint, for the patient's protection, may be used judiciously.

Support measures often prove insufficient, rendering pharmacological intervention necessary. Neuroleptics, as dopaminergic antagonists, are the drugs of choice in symptomatic control of delirium (see Table 3).

Table 3. Pharmacotherapy of delirium in oncology

	Posology	**Routes of administration**
Haloperidol	1-5 mg, every 2-12h	PO, IM, IV
Chlorpromazine	25-100 mg, every 4-12h	PO, IM, IV
Risperidone	1-3 mg, every 12h	PO, Orodisp.
Olanzapine	2.5-10 mg every 12h	Orodisp.
Quetiapine	25-100 mg, every 8h	PO

Parenteral doses are approximately twice as potent as oral doses and have more rapid onset of action. Pharmacological intervention should be particularly scrupulous in terminal patients, and reserved for situations of psychomotor agitation, hallucinations and paranoid delusions.

Dementia and cognitive deficit

In dementia the emergence of the picture is insidious or subacute, in contrast to delirium, from which it is further differentiated by the absence of changes of consciousness and by lesser disruption of sleep-wake rhythm.

Neurological and cognitive deficits attributable to tumour lesions of the CNS may be focal or global. While the former are associated with direct injury – tumoural or by radiation – to specific regions, global deficits are generally the consequence of diffuse effects (intracranial hypertension and oedema), attributable to the tumour or to treatments in progress, particularly radiotherapy (Table 4).

In addition to acute (e.g. oedema) and semi-acute reactions (e.g. demyelination), radiotherapy of brain tissue may give rise to late reactions of the encephalopathic type, which occur in approximately 28% of patients [16] and are potentially fatal or irreversible. Demential syndromes that arise after radiotherapy are of the subcortical type and ataxia and urinary incontinence are common; the estimated frequency is 3% [17].

Table 4. Post-radiotherapy organic mental syndromes

	Onset	Symptoms	Cause	Evolution
Acute	Immediate	Lethargy, headache, fever, nausea/vomiting	↑ Intracranial pressure	
Early	6 to 16 weeks	Lethargy, headache, fever, nausea/vomiting, focal neurological ss. (local RT)	Cerebral oedema? Demyelination?	Spontaneous improvement
Late	> 6 months	Focal neurological ss., headache, personality changes, seizures	Encephalopathy?	Severe and permanent

The impact of chemotherapy in cognitive terms, possibly underestimated if compared with the profusion of research into the effects of radiotherapy, has been highlighted recently. The review of neurotoxic effects of chemotherapy agents has described a variety of syndromes, such as central and peripheral neuropathies, encephalopathy, leukoencephalopathy, ototoxicity and cerebellar symptoms [9]. Even so, available information on the cognitive effects of chemotherapy is limited.

Neuropsychological studies in patients with tumours of the CNS have shown more pronounced deficits in patients with fast-growing lesions, namely glioblastoma multiforme and grade III or IV astrocytomas [18]. The laterality of lesions has also been shown to have a functional impact, lesions on the left being associated predominantly with worse results in verbal tests, while lesions of the right hemisphere are more damaging in tests of performance.

Mood disorders and anxiety

Depressive and anxiety syndromes are common in this population. By comparison with so-called 'functional' forms, patients with tumours of the CNS also show cognitive deficits that are sometimes subtle, and psychotherapeutic interventions are more difficult. In pharmacological terms, some specificities must also be noted; benzodiazepines can have paradoxical effects in these patients: low-dose antipsychotics are a viable alternative.

Corticotherapy, often administered at high doses, represents a frequent cause of affective symptoms, and psychotic conditions are also described [4]. Other common causes of anxiety and depression in oncological patients are set out below, in Tables 5 and 6 respectively.

Table 5. Causes of Anxiety in the oncological patient

SITUATIONAL	– Communication of diagnosis, discussion of prognosis – Crisis related to disease or treatment – Conflict with family member or professional – Anticipation of a frightening procedure – Waiting for results of supplementary examinations – Fear of recurrence
DISEASE-related	– Uncontrolled pain – Metabolic disturbances – Functional endocrine tumours – Paraneoplastic syndromes
TREATMENT-related	– Frightening (e.g. MRI) or painful procedures – Anxiogenic drugs (bronchodilators, antiemetics) – Withdrawal states (opioids, benzodiazepines, alcohol) – Nausea and vomiting attributable to chemotherapy
Exacerbation of PRE-EXISTING ANXIETY	– Phobia (blood, needles, claustrophobia) – Panic disorder or generalised anxiety disorder – Post traumatic stress disorder – Obsessive-compulsive disorder

(Adapted from Holland & Stiles, 2009)

Table 6. Risk factors for depression in the oncological patient

– Uncontrolled pain
– Drugs • Corticosteroids • IFN and IL-2 • Chemotherapy agents (vincristine, vinblastine, procarbazine, L-asparaginase) • Others: propanolol, tamoxifen, phenobarbital
– Metabolic disturbances • Anaemia, hypercalcaemia, ↓vit. B12, ↓folic acid
– Endocrine disturbances • Hypothyroidism (++), hyperthyroidism (-) • Adrenal insufficiency
– Paraneoplastic syndrome

(Adapted from Holland & Stiles, 2009)

Psychopharmacology

The available information on the use of psychopharmaceuticals in oncological patients comes above all from the clinical experience of liaison psychiatry teams, in the form of isolated reports or small series, and not controlled trials.

The usual approach is use of small doses *ab initio*, with a preference for drugs that have a short half-life and no metabolites.

Antipsychotics are particularly useful in situations of delirium, and in organic syndromes with behavioural changes. The detrimental effect on the seizure threshold should be taken into consideration, especially in the class of the phenothiazines (levomepromazine, chlorpromazine). Extrapyramidal symptoms, in particular akathisia, may occur, especially in patients also medicated with antiemetics like metoclopramide.

As regards the prescription of **antidepressants** (Table 7), selective serotonin reuptake inhibitors (SSRIs) represent a safe and well tolerated class of drugs. Their potential for pharmacokinetic interaction with other drugs must be acknowledged, the safest of them being escitalopram, citalopram and sertraline. Venlafaxine also represents a beneficial option in these situations. The anticholinergic effects of tricyclic antidepressants make them less appealing in neuro-oncological patients, although their sedative and antinociceptive potential can prove useful in some situations. Thanks to its dopaminergic-modulating action, bupropione can be helpful against symptoms of anergia and anhedonia; at high doses (>300mg) it tends to lower the seizure threshold, a particularly harmful effect in this population. Trazodone, at low doses – 50 to 100 mg – that are subtherapeutic in antidepressant terms, is beneficial in controlling insomnia.

Table 7. Antidepressants most widely used in oncology

	Name	Starting dose (mg)	Therapeutic dose (mg)
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram	10-20	20-60
	Escitalopram	5-10	10-20
	Fluoxetine	20	20-40
	Sertraline	25-50	50-150
Tricyclics	Amitriptyline	25-50	50-150
Other	Bupropione	150	150-300
	Mirtazapine	15	15-45
	Trazodone	50-10	150-300
	Venlafaxine	37.5-75	75-225

Use of **psychostimulants** has been described as symptomatic treatment of fatigue and asthenia. Methylphenidate, at low doses (5 to 10 mg/day, as 2 split doses), can improve levels of attention and concentration, energy and cognitive function, and the effect is particularly rapid if compared with the more delayed effect of antidepressants. Insomnia, paranoid symptoms and hallucinations can occur, generally when these drugs are used at high doses. Use of psychostimulants in patients medicated with procarbazine is contraindicated.

Benzodiazepines should be used with caution in this population, in situations of circumstantial anxiety or as coadjuvant therapy with antipsychotics when urgent sedation is required. Paradoxical effects have been reported. Drugs with a short half-life that do not undergo oxidative metabolism (e.g. lorazepam) should be preferred.

Psychotherapeutic Interventions

Psychotherapy in neuro-oncological patients tends to be supportive, drawing on crisis intervention and psychoeducational techniques [4]. Crisis intervention seeks to develop coping in the context of specific, soluble problems; its goal is a possible return to previous psychological functioning, emphasising the importance of symptomatic control as an aid to adjustment. Often, the simple expression of interest on the part of the therapist can significantly reduce distress in these patients.

Relaxation training and interventions of a cognitive-behavioural nature can be used where there is no significant cognitive compromise; they are potentially useful in controlling common symptoms that have an impact on quality of life, such as headaches [4]. In patients with limitations in terms of concentration and memory, a therapeutic diary can be used. Sessions tend to be brief, so as not to tire the patient, and a diary provides a means of writing down the key ideas addressed so that they can be revisited later.

Rehabilitation techniques have been developed to mitigate cognitive decline. In another dimension of intervention, non-verbal techniques, like music and other forms of artistic expression, can enable patients to express themselves during phases of language compromise.

The bleak prognosis often inherent makes it relevant to tackle questions related to death and preparation for death. Expressing fears and desires frequently gives the patient relief from feelings of impotence and eases the inevitable burden of family members.

Psychosocial Impact on carers

Family members of patients with tumours of the CNS face adverse situations related to brain damage. Behavioural changes can give rise to conflicts and counter-reactions with carers. The frequent loss of autonomy in such patients, who need care and supervision, tends to be exhausting for carers, most commonly spouses and other direct family members. Communication can be compromised, making the most basic interaction frustrating for patient and family members alike.

Taking these specificities into account, psychoeducation programmes have been developed for carers of patients with tumours of the CNS [19].

Provision of medical and nursing care to neuro-oncological patients is complex, demanding and potentially problematic too. Healthcare professionals often have to deal with the death of their patients, and pathological reactions of loss are not uncommon [20]. Management of terminal care can be disturbing, and particularly therapeutic decisions in patients who are confused or whose awareness is compromised.

Some practices have been presented as beneficial in minimising the psychosocial impact on professionals. Examples are the practice of frequent rotations, particularly of nursing staff, and the existence of multidisciplinary support groups for professionals [21].

Conclusion

Psychiatric symptoms may be the only manifestation of brain tumours. Because of the high degree of non-specificity of the symptomatology caused, such tumours may be confused at an early stage with so-called functional psychiatric disorders. Thus a careful clinical assessment associated with the presence of atypical characteristics at the time of presentation of symptomatology should prompt additional investigation, with recourse in particular to imaging examinations. Treatment of psychiatric symptoms is based on recourse to psychopharmaceuticals, with antipsychotics at the top of the list, psychotherapy and psychoeducation for carers.

Studying the symptomatology caused by tumours of the CNS may lead to a better understanding of the physiopathology of psychiatric disorders, categorisation of diagnoses and development of new and better forms of treatment.

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