Neuro-oncology

Neuro-oncology research in the UK is a truly multidisciplinary endeavour and each year the annual British Neuro-oncology Society (BNOS) meeting reflects this in its mix of delegates from all clinical and research specialties in the field and in the participation of many of the neuro-oncology charities. In 2010 the BNOS Young Investigator Award was introduced to reward early researchers who have made a notable contribution to the field. Already, in only its second year, the award has become a reflection of the broad scope of neuro-oncology research in the UK. In 2010, Dr Sara Piccirillo was rewarded for her laboratory based work examining stem cells in glioma. This year's richly deserved recipient of the **BNOS Young Investigator Award**, once again supported by the charity Brain Tumour UK, is Dr Ally Rooney from Edinburgh, whose following article provides background to his work in the clinics researching psychological symptoms in Brain tumour patients.

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Challenges and Opportunities in Psychological Neuro-oncology

In 2007 I was recruited by NHS Lothian to study clinical depression in adults with cerebral glioma. Since then I have been fortunate to participate in a variety of neuro-oncology conferences and projects, and to study the mental health of glioma patients under the supervision of Dr Robin Grant (Neurologist) and Dr Alan Carson (Neuropsychiatrist). Data from our original research will be published over the coming year [1]. This article briefly outlines a personal view of current challenges and opportunities in the field of psychological neuro-oncology.

"Why bother?"

A few years ago I applied for funding to study clinical depression in glioma patients. The interviewer opened with, "Why bother? We know what you're going to find – we know enough about depression in cancer already." Indeed a quick MEDLINE search combining the keywords "depression" and "cancer" identifies over 6000 titles. Yet it would be premature to assume that conclusions drawn from studies of depression in patients with systemic cancer will translate accurately to patients with brain cancer. Glioma is an infiltrative tumour affecting the organ primarily implicated in depression. A greater burden of epilepsy, neurological deficit, cognitive impairment, and often, mortality is observed in glioma than in systemic cancer. Like the interviewer, some readers may believe that studying depression in glioma may be re-treading old ground. Nevertheless, psychological complications should specifically be studied in neuro-oncology, because, as others also have argued [2], these patients are qualitatively distinct.

Clinical nihilism

The interviewer persisted, "But what's the point? I'd be depressed if I had a brain tumour". Yet we must avoid conflating the colloquial meaning of 'depressed' (sad), with its medical meanings (variably: clinical depression; Major Depressive Disorder; or significant depressive symptoms on a rating scale). In fact, after adjusting to the diagnosis, most glioma patients are not clinically depressed [3] or even generally distressed [4]. Despite clear evidence that most glioma patients cope remarkably well, some may think that clinically significant psychological distress is to be expected, and, by implication, tolerated. This is strange. Few cardiologists would say, "Of course he's having a heart attack – he's a fat smoker who takes no exercise", and then provide no treatment. Would anyone realistically say, "Of course he's depressed – he's got a brain tumour"? Sadly, it appears that they might. In our questionnaire vignette survey of over 100 consultants working in neuro-oncology-related subspecialties in Scotland, a large proportion of respondents (39%) dismissed cardinal symptoms of clinical depression as simply "an understandable reaction" to having a glioma. These doctors were much less likely to recommend treatment with antidepressants [5]. In a separate and currently unpublished survey, 78% of our glioma patients' GPs agreed with the statement, "Most depression is a normal reaction to having glioma". Such attitudes may extend to service planning. In a third, ongoing survey, conducted in collaboration with colleagues in Cambridge, only 43% of neuro-oncology multi-disciplinary teams (MDTs) in the UK reported having access to neuropsychiatry services. Researchers working in this field face the challenge of changing attitudes. We can, however, remind colleagues that the psychological consequences of glioma range in severity from minimal to profound. Profound and persistent symptoms are not normal. Such mental ill-health is potentially treatable.

Psychological complications should specifically be studied in neuro-oncology

Theoretical difficulties

Clinical depression cannot be diagnosed using a brain scan or blood test. This might seem inconvenient, and if so it is testimony to the extent to which we have become used to thinking of depression as a disease with a clearly defined pathogenesis. In fact, the term "clinical depression" is more of a convention; a convenient label that we currently attach to a group of symptoms that are hypothesised to co-vary together. There is no single pathophysiology underlying these symptoms; depression is not a disease in that sense [6]. Sometimes the symptoms that contribute to a diagnosis of clinical depression could be caused by grief, or occur as a side effect of glioma treatment. It is a matter of ongoing academic debate how to distinguish appropriately between 'disordered sadness' (essentially clinical depression) and the normal processes of adjustment to loss. Classically the loss cited in this debate is bereavement, but I think that losses of health, independence, identity, and hopes that can accompany a diagnosis of glioma are also relevant. The fundamental issue is what we should call "disorder" in this context. It is a difficult and abstract debate that muddies the message for clinicians, and, in my experience, can confuse patients totally. Yet the question of what level of distress or sadness to call "normal" is inescapable in neuro-oncology, where losses accrue as disease progresses. At some point we will have to face it, which is precisely why more research is now needed.

Lack of basic research

As we currently understand it, clinical depression is consistently associated with impaired quality of life (QOL) in glioma [3]. With best treatment for glioblastoma multiforme conferring a median survival of only 14 months [7], seeking to maximise QOL is at least humane, and may be the primary therapeutic aim in patients with inoperable or end-stage tumours. Evidence-based care would require that psychological complications arising in adults with glioma are thoroughly researched and understood. Yet scientific knowledge about clinical depression in glioma is really quite limited. Older studies (pre-1980) of the psychiatric consequences of cerebral tumours are mostly now of historic interest. They were generally conducted before the advent of CT/MRI scanning, in highly selected populations, using diagnostic classification systems which differed considerably from those in use today. Since 1980, around 40 observational studies have examined the relationship between depression and glioma. We reviewed this literature and found most of these studies are small ($n < 100$ patients) and cross-sectional in design. Many have important limitations of methodology or study reporting. The most replicated findings relating to depression in glioma are that it occurs frequently enough to be clinically significant (median prevalence = 19%), and is associated with functional impairment, impaired QOL, and, possibly, increased mortality [3]. Little else is clear at present. When it comes to more severe psychiatric symptoms, such as psychosis affecting neuro-oncology patients, the English-language literature consists almost entirely of case reports (source: personal systematic search).

Poor evidence for treatment

This uncertainty extends to treatment of the psychological complications of glioma. In a population at such high risk of epilepsy, fatigue, and cognitive impairment, there is enough clinical equipoise to justify a randomised controlled trial (RCT) of antidepressants for depression in glioma. However, none has been completed and the pharmacological treatment of depression in glioma entirely lacks a robust evidence base [8]. Do antidepressants still improve mood with a tumour disrupting the brain? Do they improve or worsen epilepsy? The answers to these questions currently are unknown. There is also little evidence to inform the choice of psychotherapeutic treatment [9], a relevant question in cognitively impaired patients, although interest in this area is increasing. The lack of treatment trials was affirmed for me at a recent European neuro-oncology conference. I observed the main symposia to consist mostly of reports of RCTs of various exciting tumour treatments. The QOL session, by contrast, was entirely filled with reports of observational studies. Although valuable, observational research can be difficult to interpret in neuro-oncology because of the large number of potential confounders. QOL researchers could move beyond descriptive studies towards seeking effective treatments.

Practical difficulties

The general lack of evidence may have less to do with an absence of psychopathology and more to do with the practical difficulties of studying these patients. Glioma is a relatively rare cancer and psychological complications of glioma rarer still. Multicentre studies will be necessary to boost recruitment, yet Cancer Research UK – previously a major funder – currently has chosen not to fund any psychosocial research [10], making such complicated and expensive projects harder to complete. Glioma patients are also difficult to recruit to clinical research studies in a timely manner: in a relatively high-quality study, only 75/91 eligible patients could be approached within three months of diagnosis [11]. In those that are fit and happy enough to participate in studies of mental health, a degree of selection bias is inevitable. Among participants, high attrition is the norm as many patients become disabled or die as a result of progressive disease.

Charity involvement

Although these are significant challenges, it is possible to minimise their impact. There are a number of opportunities here. For example, the brain tumour charity sector potentially may have an influential role to play in the coming years. Together with the British Neuro-Oncology Society (BNOS), Brain Tumour UK kindly sponsors an annual Young Investigator award, supporting articles like this. On a more fundamental level, many of the charities have a strong interest in improving the psychological care of patients and carers, for whom they are a valuable source of information and support. There will often be alignment between charitable aims and those of researchers in psychological neuro-oncology. Charities can comment on and strengthen research proposals. They can also influence clinical initiatives: for example in Edinburgh, Brain Tumour Action recently provided funding to allow neuroscience nurses to attend training in the clinical care of neuro-oncology patients. The charities are politically active and are a potentially powerful lobby. In general, maintaining close links with brain tumour charities should create future opportunities to systematically improve the psychological care of their patients.

National and international initiatives

The Scottish Adult Neuro-Oncology Network (SANON) is a Managed Clinical Network set up to facilitate interaction between the disciplines contributing to the care of neuro-oncology patients in Scotland. Currently I chair the SANON Supportive and Psychological Care subgroup which is working on a number of projects. At the international level, I was lucky enough to work with the Brain Tumour Alliance Australia and 'beyondblue', an Australian depression charity, to produce an information leaflet specifically on depression and anxiety in patients with a brain tumour [12]. These initiatives show that national and international collaborative opportunities exist to be grasped.

Role of psychiatry

Conferences should present an ideal opportunity to meet other researchers in this exciting field. BNOS has an annual multidisciplinary conference (the next one is scheduled for Manchester in July 2012) and the European Association for Neuro-Oncology and World Federation for Neuro-Oncology have biannual and quadrennial conference cycles, respectively. I have, however, been struck by the absence of psychiatrists at these conferences. Neuro-oncology intersects many medical specialties. With relatively high levels of depression and distress in glioma compared to other patient groups, and a complex interplay of stressors, psychiatry has a strong case to be included under the neuro-oncology umbrella.

As discussed, diagnosing mental disorder in patients with glioma is not always straightforward. Psychiatric input could be useful to help navigate the latest theoretical systems. For example, the two global psychiatric diagnostic classification schemes are the American Psychiatric Association's

Diagnostic and Statistical Manual of mental disorders (DSM) and the World Health Organisation's International Classification of Disease (ICD). Both systems are preparing new editions for publication in the next few years (DSM-5 and ICD-11, respectively). Psychiatrists could play an important specialist role interpreting these new systems for a neuro-oncology audience, applying them clinically, and testing them in rigorous research. Increased psychiatric input would surely benefit neuro-oncology as a speciality.

In the UK MDT survey reported earlier, where most MDTs had no access to neuropsychiatry, 82% of them perceived an unmet need for psychiatry in neuro-oncology.

Potential impact

Perhaps the biggest opportunity is simply the current relative lack of evidence underpinning the psychological care of neuro-oncology patients. This is a field waiting to be explored. Relevant questions include how to differentiate between normal and disordered emotional reactions in the context of neuro-oncological disease, the longitudinal course of various mental disorders, and the relative benefits and harms of a variety of treatments – and there are many others. There probably needs to be a rebalancing of research methodology towards treatment trials, without losing observational research entirely. Psychological neuro-oncology is a young and exciting field in which clinical research could make a big difference to the future care of patients and their relatives. ■

References

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Useful websites

BNOS www.bnos.org.uk
SANON www.neurooncology.scot.nhs.uk
Brain tumour umbrella charity: www.braintumourresearch.org

Learning points

- Psychological neuro-oncology is the field of studying the mental consequences of neuro-oncological diseases.
- Psychological symptoms vary in severity and, while some distress can be normal, severe symptoms generally are not.
- There is little high-quality evidence about the management of mental ill-health in these patients.
- There may be a role for psychiatrists in future research, diagnosis, and treatment in this field.
- Brain tumour charities are a useful source of information for patients and carers and, potentially, of funding for researchers.